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Use of substituted 2,5-diamidoindoles for the treatment of urological diseases

5 The present invention relates to the use of 2,5-diamidoindole derivatives for the preparation of medicaments for treating urological disorders in humans and/or animals.

10 Endothelial cells and a large number of other cell types produce endothelin (ET), a polypeptide hormone having 21 amino acid residues. Endothelin is a potent vasoconstrictor formed from the prohormone "Big Endothelin" (bET, 38 amino acid residues) by cleavage of the peptide bond between Trp 21 and Val 22. The conversion of prohormone bET into the active form ET is effected by a metalloprotease, the endothelin-converting enzyme (ECE). Inhibition of ECE thus prevents the conversion of bET into biologically active ET.

15 ET is a potent constrictor of arterial and venous vessels. Accordingly, it has to be assumed that abnormal ET levels are directly involved in the pathophysiology of various disorders. Elevated endothelin levels are observed in cardiovascular disorders such as essential, pulmonary and malignant hypertension, in advanced atherosclerosis, myocardial infarction, heart and kidney failure (Miyachi T, Masaki T.; Pathophysiology of endothelin in the cardiovascular system. Annu Rev Physiol. 20 1999; 61:391-415). Additional indications are obtained from the analysis of different animal models for ischaemic disorders such as angina pectoris, myocardial infarction and stroke and for cardiac arrhythmia and renal dysfunction. In these different syndromes, the reduction of ET levels results in a reduction of pathological parameters.

25 The physiological role of endothelin in urological tissues, such as prostate and bladder, has been suggested in several studies. Endothelin is known to contract rabbit bladder and urethra smooth muscle [Garcia-Pascual, A. et al, Acta Physiol Scand. 30 140: 545, 1990.], rat prostate smooth muscle [Salamoussa, A. et al, Eur J Pharmacol.

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403: 139, 2000], human detrusor smooth muscle [Okamoto-Koizumi, T. et al, Clin Sci (Lond). 96: 397, 1999] and human prostate smooth muscle [Ishigooka M. et al, Eur Urol. 37: 494 – 498, 2000]. In addition to the contribution to basal smooth muscle tone, the regulation of the human prostatic cell growth by endothelin was reported. [Walden P. D. et al, Prostate 34: 241, 1998] The pathological role of the endothelin in urological disease such as benign prostatic hyperplasia (BPH) has been investigated in experimental animal models. The increase in expression of endothelin receptor has been observed in bladder smooth muscle cells isolated from a rabbit model of bladder outlet obstruction (BOO) [Khan, M. A. et al, Urol Res. 27: 445, 1999] and prostate isolated from castrated rats [Takahashi W et al, Naunyn-Schmiedeberg's Arch Pharmacol. 366: 166, 2002]. These evidences suggest a pathological role for endothelin in the BOO as frequently observed in human BPH patients. Furthermore, physiological role of ECE has been reported in human and rabbit urinary bladder [Saenz De Tejada, I. et al, J Urol. 148: 1290, 1992] and rat prostate. [Takahashi W et al, Naunyn-Schmiedeberg's Arch Pharmacol. 366: 166, 2002].

The present invention is now directed to the treatment of urological disorders with ECE inhibitors that leads to an improvement of these disorders.

It is an object of the present invention to provide medicaments for treating urological disorders, in particular benign prostatic hyperplasia and overactive bladder.

The object of the present invention is achieved by compounds which act as ECE inhibitors. Preferred compounds that act as ECE inhibitors are compounds of the formula (I).

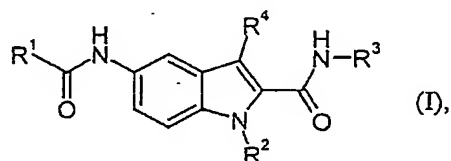
Compounds of a similar structure are known in other indications or for other mechanisms of action. Thus, for example, WO 99/33800 describes indole derivatives as factor Xa inhibitors, WO 94/14434 describes indole derivatives as endothelin

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receptor antagonists and EP-A 0 655 439 describes glycoprotein IIB/IIIa antagonists for inhibiting platelet aggregation.

The present invention provides compounds of the formula (I)

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in which

R¹ represents (C₅-C₁₅)-alkyl, (C₅-C₁₅)-alkenyl or (CH₂)_nG,

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in which

G represents cycloalkyl or represents a 5- or 6-membered heterocycle having one or two oxygen atoms,

15

n represents 0 to 4 and

alkyl, alkenyl and G are optionally substituted by 1 to 3 substituents, independently of one another selected from the group consisting of halogen, hydroxyl, trifluoromethyl, trifluoromethoxy, cyano, nitro, alkyl, alkoxy, alkylthio, carboxyl, alkoxycarbonyl, amino, alkylamino, alkylcarbonylamino and alkylaminocarbonyl,

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R² represents (C₁-C₈)-alkyl, (CH₂)_mcycloalkyl, (CH₂)_mheterocyclyl, (CH₂)_maryl or (CH₂)_mheteroaryl,

25

in which

- 4 -

m represents 0 to 4 and

alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are optionally substituted by 1 to 3 substituents, independently of one another selected from the group consisting of halogen, hydroxyl, trifluoromethyl, trifluoromethoxy, cyano, nitro, alkyl, alkoxy, alkylthio, alkoxycarbonyl, amino, alkylamino, alkylcarbonylamino, alkylaminocarbonyl, alkylaminosulphonyl and alkylsulphonylamino,

10 R^3 represents $(CH_2)_o$ cycloalkyl, $(CH_2)_o$ heterocyclyl, $(CH_2)_o$ aryl or $(CH_2)_o$ heteroaryl,

in which

15 o represents 0 to 4 and

cycloalkyl, heterocyclyl, aryl and heteroaryl are optionally substituted by 1 to 3 substituents, independently of one another selected from the group consisting of halogen, hydroxyl, trifluoromethyl, trifluoromethoxy, cyano, nitro, alkyl, alkoxy, alkylthio, hydroxycarbonyl, alkoxycarbonyl, amino, alkylamino, alkylcarbonylamino, alkylaminocarbonyl, alkylaminosulphonyl and alkylsulphonylamino,

25 R^4 represents hydrogen, (C_1-C_4) -alkyl, $(CH_2)_p$ cycloalkyl, $(CH_2)_p$ heterocyclyl, $(CH_2)_p$ aryl or $(CH_2)_p$ heteroaryl,

in which

30 p represents 0 to 4 and

alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are optionally substituted by 1 to 3 substituents, independently of one another selected from the group consisting of halogen, hydroxyl, trifluoromethyl, trifluoromethoxy, cyano, nitro, alkyl, alkoxy, alkylthio, hydroxycarbonyl, alkoxy carbonyl, amino, 5 alkylamino, alkylcarbonylamino, alkylaminocarbonyl, alkylaminosulphonyl and alkylsulphonylamino,

and their salts, hydrates, hydrates of the salts and solvates,

10 for the production of a medicament for the prophylaxis and/or treatment of urological diseases.

Depending on the substitution pattern, the compounds of the formula (I) can exist in stereoisomeric forms which either relate to each other as image and mirror image 15 (enantiomers) or do not relate to each other as image and mirror image (diastereomers). The invention relates both to the enantiomers or diastereomers and to their respective mixtures. The racemic forms can be separated, in a known manner, in exactly the same way as the diastereomers, into the stereoisomerically uniform constituents. Equally, the present invention also relates to the other tautomers of the compounds of the 20 formula (I) and their salts.

Salts of the compounds of the formula (I) can be physiologically acceptable salts of the compounds according to the invention with mineral acids, carboxylic acids or sulphonic acids. Particular preference is given, for example, to salts with hydrochloric 25 acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, ethanesulphonic acid, toluenesulphonic acid, benzenesulphonic acid, naphthalene-disulphonic acid, trifluoroacetic acid, acetic acid, propionic acid, lactic acid, tartaric acid, citric acid, fumaric acid, maleic acid or benzoic acid.

30 Salts which may also be mentioned are salts with customary bases, for example alkali metal salts (e.g. sodium salts or potassium salts), alkaline earth metal salts (e.g. calcium

salts or magnesium salts) or ammonium salts which are derived from ammonia or organic amines such as diethylamine, triethylamine, ethyldiisopropylamine, procaine, dibenzylamine, N-methylmorpholine, dihydroabietylamine, 1-phenamine or methyl-piperidine.

5

According to the invention, those forms of the compounds of the formula (I) which, in the solid or liquid state, form a molecule compound or a complex by hydration with water or coordination with solvent molecules are termed hydrates and solvates, respectively. Examples of hydrates are sesquihydrates, monohydrates, dihydrates and trihydrates. In precisely the same way, the hydrates or solvates of salts of the compounds according to the invention also come into consideration.

10

In addition, the invention also encompasses prodrugs of the compounds according to the invention. According to the invention, those forms of the compounds of the formula (I) which may themselves be biologically active or inactive but which can be converted (for example metabolically or solvolytically) into the corresponding biologically active form under physiological conditions are termed prodrugs.

15

Within the context of the present invention, the substituents have, unless otherwise indicated, the following meaning:

20

Alkyl represents straight-chain or branched alkyl and comprises, unless indicated otherwise, C₁-C₆-alkyl, in particular methyl, ethyl, propyl, isopropyl, butyl, isobutyl.

C₅-C₁₅)-Alkyl, (C₁-C₈)-alkyl, (C₁-C₄)-alkyl represents straight-chain or branched alkyl having 5 to 15, 1 to 8 and 1 to 4 carbon atoms, respectively. The following radicals may be mentioned by way of example and by way of preference: neopentyl, isoamyl.

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Cycloalkyl comprises saturated hydrocarbon radicals having up to 14 carbon atoms, i.e. monocyclic C₃-C₁₂-cycloalkyl, preferably C₃-C₈-cycloalkyl, such as, for example,

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cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, and polycyclic alkyl, i.e. preferably bicyclic and tricyclic, optionally spirocyclic C₇-C₁₄-cycloalkyl, such as, for example, bicyclo[2.2.1]-hept-1-yl, bicyclo[2.2.1]-hept-2-yl, bicyclo[2.2.1]-hept-7-yl, bicyclo[2.2.2]-oct-2-yl, bicyclo-
5 [3.2.1]-oct-2-yl, bicyclo[3.2.2]-non-2-yl and adamantyl.

Aryl represents an aromatic radical having 6 to 10 carbon atoms. Preferred aryl radicals are phenyl and naphthyl.

10 Alkoxy represents a straight-chain or branched alkyl radical having in particular 1 to 6, 1 to 4 or 1 to 3 carbon atoms which is attached via an oxygen atom. Preference is given to a straight-chain or branched alkoxy radical having 1 to 3 carbon atoms. The following radicals may be mentioned by way of example and by way of preference: methoxy, ethoxy, n-propoxy, isopropoxy, t-butoxy, n-pentoxy and n-hexoxy.

15 Alkylthio represents a straight-chain or branched alkyl radical having in particular 1 to 6, 1 to 4 or 1 to 3 carbon atoms which is attached via a sulphur atom. Preference is given to a straight-chain or branched alkylthio radical having 1 to 3 carbon atoms. The following radicals may be mentioned by way of example and by way of
20 preference: methylthio, ethylthio, n-propylthio, isopropylthio, t-butylthio, n-pentylthio and n-hexylthio.

Alkoxycarbonyl represents a straight-chain or branched alkoxy radical having 1 to 6 or 1 to 4 carbon atoms which is attached via a carbonyl group. Preference is given to
25 a straight-chain or branched alkoxycarbonyl radical having 1 to 4 carbon atoms. The following radicals may be mentioned by way of example and by way of preference: methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, isopropoxycarbonyl and t-butoxycarbonyl.

30 Alkylamino represents an amino group which has one straight-chain or branched or two identical or different straight-chain or branched alkyl substituents having

preferably in each case 1 to 6, 1 to 4 or 1 to 2 carbon atoms. Preference is given to straight-chain or branched alkylamino radicals having in each case 1 to 4 carbon atoms. The following radicals may be mentioned by way of example and by way of preference: methylamino, ethylamino, n-propylamino, isopropylamino, t-butylamino, 5 n-pentylamino, n-hexylamino, *N,N*-dimethylamino, *N,N*-diethylamino, *N*-ethyl-*N*-methylamino, *N*-methyl-*N*-n-propylamino, *N*-isopropyl-*N*-n-propylamino, *N*-t-butyl-*N*-methylamino, *N*-ethyl-*N*-n-pentylamino and *N*-n-hexyl-*N*-methylamino.

Alkylcarbonylamino (acylamino) represents, in the context of the invention, an 10 amino group having a straight-chain or branched alkyl radical which is attached via a carbonyl group and has preferably 1 to 6, 1 to 4 or 1 to 2 carbon atoms. Preference is given to a monoacylamino radical having 1 to 2 carbon atoms. The following radicals may be mentioned by way of example and by way of preference: acetamido, propionamido, n-butyramido and pivaloylamido.

15 Alkylaminocarbonyl represents an amino group which is attached via a carbonyl group and has one straight-chain or branched or two identical or different straight-chain or branched alkyl substituents having preferably in each case 1 to 4 or 1 to 2 carbon atoms. The following radicals may be mentioned by way of example and by 20 way of preference: methylaminocarbonyl, ethylaminocarbonyl, isopropyl aminocarbonyl, t-butylaminocarbonyl, *N,N*-dimethylaminocarbonyl, *N,N*-diethylaminocarbonyl, *N*-ethyl-*N*-methylaminocarbonyl and *N*-t-butyl-*N*-methylaminocarbonyl.

Heteroaryl represents a 5- to 10-membered aromatic heterocycle having up to 3 25 heteroatoms from the group consisting of S, O and/or N. The following radicals may be mentioned by way of example and by way of preference: pyridyl, pyrimidyl, thienyl, furyl, pyrrolyl, thiazolyl, N-triazolyl, oxazolyl or imidazolyl. Preference is given to pyridyl, furyl, thiazolyl and N-triazolyl.

30 Heterocyclyl represents a 3- to 8-membered saturated or partially unsaturated heterocycle which may contain up to 3 heteroatoms from the group consisting of S, O and

N and which may be attached via a nitrogen atom. The following radicals may be mentioned by way of example and by way of preference: morpholinyl, piperidinyl, piperazinyl, methylpiperazinyl, thiomorpholinyl, pyrrolidinyl, and also 3-, 7- and 8-membered heterocycles, such as, for example, aziridines (for example 1-azacyclopropan-1-yl), azetidines (for example 1-azacyclobutan-1-yl) and azepines (for example 1-azepan-1-yl). The unsaturated representatives may contain 1 or 2 double bonds in the ring.

Halogen represents fluorine, chlorine, bromine or iodine, with fluorine and chlorine being preferred, unless indicated otherwise.

Alkylaminosulphonyl represents an amino group which is attached via a sulphonyl group and which has one straight-chain or branched or two identical or different straight-chain or branched alkyl substituents having preferably 1 to 4 or 1 to 2 carbon atoms. The following radicals may be mentioned by way of example and by way of preference: methylaminosulphonyl, ethylaminosulphonyl, isopropylaminosulphonyl, t-butylaminosulphonyl, *N,N*-dimethylaminosulphonyl, *N,N*-diethylaminosulphonyl, *N*-ethyl-*N*-methylaminosulphonyl and *N*-t-butyl-*N*-methylaminosulphonyl.

Alkylsulphonylamino represents a sulphonyl group which is attached via an amino group and which has one straight-chain or branched alkyl substituent having preferably 1 to 4 or 1 to 2 carbon atoms. The following radicals may be mentioned by way of example and by way of preference: methylsulphonylamino, ethylsulphonylamino, isopropylsulphonylamino, t-butylsulphonylamino.

The abovementioned general or preferred radical definitions apply both to the end products of the formula (I) and, correspondingly, to the starting materials or intermediates required in each case for the preparation.

Preference is given to compounds of the formula (I) in which

- 10 -

R¹ represents (C₅-C₁₅)-alkyl or (CH₂)_ncycloalkyl,

in which

5 n represents 0 to 4 and

alkyl and cycloalkyl are optionally substituted by 1 to 3 substituents, independently of one another selected from the group consisting of halogen, hydroxyl, trifluoromethyl, trifluoromethoxy, cyano, nitro, alkyl, alkoxy, 10 alkylthio, carboxyl, alkoxycarbonyl, alkyl carbonylamino and alkylamino-carbonyl,

R² represents (C₁-C₈)-alkyl, (CH₂)_mcycloalkyl, (CH₂)_mheterocyclyl, (CH₂)_maryl or (CH₂)_mheteroaryl,

15

in which

m represents 0 to 4 and

20 alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are optionally substituted by 1 to 3 substituents, independently of one another selected from the group consisting of halogen, hydroxyl, trifluoromethyl, trifluoromethoxy, cyano, nitro, alkyl, alkoxy, alkylthio, alkoxycarbonyl, amino, alkylamino, alkyl-carbonylamino, alkylaminocarbonyl, alkylaminosulphonyl and alkyl- 25 sulphonylamino,

R³ represents (CH₂)_ocycloalkyl, (CH₂)_oheterocyclyl, (CH₂)_oaryl or (CH₂)_ohetero-aryl,

30 in which

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o represents 0 to 4 and

cycloalkyl, heterocyclyl, aryl and heteroaryl are optionally substituted by 1 to 3 substituents, independently of one another selected from the group consisting of halogen, hydroxyl, trifluoromethyl, trifluoromethoxy, cyano, nitro, alkyl, alkoxy, alkylthio, hydroxycarbonyl, alkoxycarbonyl, amino, alkylamino, alkylcarbonylamino, alkylaminocarbonyl, alkylaminosulphonyl and alkylsulphonylamino,

10 R⁴ represents hydrogen, (C₁-C₄)-alkyl, (CH₂)_pcycloalkyl, (CH₂)_pheterocyclyl, (CH₂)_paryl or (CH₂)_pheteroaryl,

in which

15 p represents 0 to 4 and

alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are optionally substituted by 1 to 3 substituents, independently of one another selected from the group consisting of halogen, hydroxyl, trifluoromethyl, trifluoromethoxy, cyano, nitro, alkyl, alkoxy, alkylthio, hydroxycarbonyl, alkoxycarbonyl, amino, alkylamino, alkylcarbonylamino, alkylaminocarbonyl, alkylaminosulphonyl and alkylsulphonylamino,

and their salts, hydrates, hydrates of the salts and solvates.

25

Particular preference is given to compounds of the formula (I) in which

30 R¹ represents neopentyl, (bicyclo[2.2.1]heptyl)methyl, cyclohexylmethyl, cyclobutylmethyl, cyclopentylmethyl, 2,2-dimethyl-1-butyl, 2-ethyl-2-methyl-1-butyl, (1-methylcyclopentyl)methyl, 1-methylcyclohexyl, 4-hydroxy-2,2-dimethyl-1-butyl or 2,2-dimethyl-1-but-3-enyl,

5 R^2 represents (C₁-C₄)-alkyl which may be substituted by hydroxyl or fluorine or represents benzyl which is optionally substituted by 1 or 2 substituents, independently of one another selected from the group consisting of fluorine, chlorine, bromine, methyl and trifluoromethyl,

10 R^3 represents phenyl, pyridyl or pyrimidyl which for their part are optionally substituted by a substituent selected from the group consisting of fluorine, chlorine, trifluoromethyl, methyl, ethyl, methoxy, ethoxy, n-propoxy, isopropoxy, amino, hydroxyl, hydroxycarbonyl, (C₁-C₃)-alkylcarbonylamino and mono-(C₁-C₄)-alkylaminocarbonyl,

15 R^4 represents hydrogen

and their salts, hydrates, hydrates of the salts and solvates.

Preference is given to compounds of the formula (I) in which

20 R^1 represents neopentyl.

Preference is also given to compounds of the formula (I) in which

25 R^2 represents benzyl which may be substituted up to two times, independently of one another, by alkyl or halogen, preferably fluorine.

Preference is also given to compounds of the formula (I) in which

30 R^3 represents phenyl which may be substituted up to two times, independently of one another, by alkyl or alkoxy.

Preference is also given to compounds of the formula (I) in which

- 13 -

R³ represents phenyl, pyridyl or pyrimidyl,

5 which for their part are optionally substituted by a substituent selected from the group consisting of fluorine, chlorine, trifluoromethyl, methyl, ethyl, methoxy, ethoxy, n-propoxy, isopropoxy, amino, hydroxyl, hydroxycarbonyl, (C₁-C₃)-alkylcarbonylamino and mono-(C₁-C₄)-alkylaminocarbonyl.

10 Preference is also given to compounds of the formula (I) in which

R⁴ represents hydrogen.

Preference is also given to compounds of the formula (I)

15 in which

R¹ represents (C₅-C₁₀)-alkyl or (CH₂)_n(C₄-C₇)-cycloalkyl, preferably (CH₂)_n-cyclobutyl, (CH₂)_ncyclopentyl, (CH₂)_ncyclohexyl or (CH₂)_nbicyclo[2.2.1]-heptyl,

20 in which

n represents 1 to 3 and

25 alkyl and cycloalkyl are optionally substituted by 1 to 3 substituents, independently of one another selected from the group consisting of halogen, hydroxyl, trifluoromethyl, trifluoromethoxy, cyano, nitro, alkyl, alkoxy, alkylthio, carboxyl, alkoxycarbonyl, alkylcarbonylamino and alkylamino-carbonyl,

30 R² represents (C₁-C₄)-alkyl, (CH₂)_mcycloalkyl or (CH₂)_maryl,

- 14 -

in which

m represents 0 to 4 and

5

alkyl, cycloalkyl and aryl are optionally substituted by 1 to 3 substituents, independently of one another selected from the group consisting of halogen, trifluoromethyl, cyano, nitro, alkyl, alkoxy, amino, alkylamino, alkyl-carbonylamino and alkylaminocarbonyl,

10

R³ represents (CH₂)_oaryl or (CH₂)_oheteroaryl,

in which

15

o represents 0 to 3 and

aryl and heteroaryl are optionally substituted by 1 to 3 substituents, independently of one another selected from the group consisting of halogen, trifluoromethyl, cyano, nitro, alkyl, alkoxy, amino, alkylamino, alkyl-carbonylamino and alkylaminocarbonyl,

20

R⁴ represents hydrogen, (C₁-C₄)-alkyl or (CH₂)_paryl,

in which

25

p represents 1 to 4 and

alkyl and aryl are optionally substituted by 1 to 3 substituents, independently of one another selected from the group consisting of halogen, trifluoromethyl, cyano, nitro, alkyl, alkoxy, alkylcarbonylamino and alkylaminocarbonyl,

30

and their salts, hydrates, hydrates of the salts and solvates.

Particular preference is given to compounds of the formula (I)

5 in which

R^1 represents neopentyl, bicyclo[2.2.1]heptyl, cyclohexylmethyl, cyclobutylmethyl, cyclopentylmethyl, 2,2-dimethyl-4-butyl, 2,2-dimethyl-1-butyl or 2-ethyl-2-methyl-1-butyl, which for their part are optionally substituted by 1 to
10 2 substituents, independently of one another selected from the group consisting of halogen, cyano, alkyl, alkoxy, alkylcarbonylamino and alkylaminocarbonyl,

R^2 represents (C₁-C₄)-alkyl or (CH₂)_mphenyl,
15

in which

m represents 0 to 4 and

20 alkyl and phenyl are optionally substituted by 1 to 2 substituents, independently of one another selected from the group consisting of halogen, trifluoromethyl, cyano, alkyl, alkoxy, alkylcarbonylamino and alkylaminocarbonyl,

25 R^3 represents (CH₂)_ophenyl, (CH₂)_opyridyl, (CH₂)_othienyl or (CH₂)_opyrimidyl,

in which

o represents 0 to 3 and
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phenyl, pyridyl, thienyl and pyrimidyl for their part are optionally substituted by 1 to 3 substituents, independently of one another selected from the group consisting of halogen, trifluoromethyl, cyano, nitro, alkyl, alkoxy, alkyl-carbonylamino and alkylaminocarbonyl,

5

R^4 represents hydrogen or (C_1-C_4) -alkyl,

10

in which alkyl is optionally substituted by 1 to 3 substituents, independently of one another selected from the group consisting of halogen and trifluoromethyl,

and their salts, hydrates, hydrates of the salts and solvates.

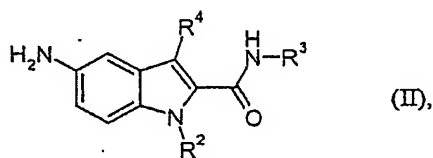
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Particular preference is also given to combinations of two or more of the preferred ranges mentioned above.

The present invention also provides a process for preparing the compounds of the formula (I), characterized in that either

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[A] compounds of the formula (II)



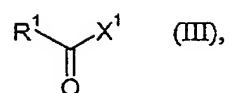
in which

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R^2 , R^3 and R^4 are as defined above,

are reacted with compounds of the formula (III)

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in which

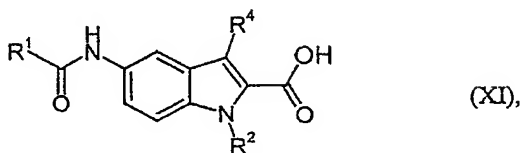
R^1 is as defined above and

5

X^1 represents halogen, preferably bromine or chlorine, or hydroxyl,

or

10 [B] compounds of the formula (XI)



in which

15 R^1 , R^2 and R^4 are as defined above,

are reacted with compounds of the formula (VI)



20 in which

R^3 is as defined above,

to give compounds of the formula (I).

25

If X^1 represents halogen, the reaction in process A is carried out in inert solvents, if appropriate in the presence of a base, preferably in the temperature range of from 0°C to 50°C at atmospheric pressure.

5 Suitable inert solvents are, for example, halogenated hydrocarbons, such as methylene chloride, trichloromethane, carbon tetrachloride, trichloroethane, tetrachloroethane, 1,2-dichloroethane or trichloroethylene, ethers, such as diethyl ether, methyl tert-butyl ether, dioxane, tetrahydrofuran, glycol dimethyl ether or diethylene glycol dimethyl ether, hydrocarbons, such as benzene, xylene, toluene, hexane, 10 cyclohexane or mineral oil fractions, or other solvents, such as nitromethane, ethyl acetate, acetone, dimethylformamide, dimethylacetamide, 1,2-dimethoxyethane, 2-butanone, dimethyl sulphoxide, acetonitrile, pyridine or hexamethylphosphoric triamide; preference is given to dioxane or methylene chloride.

15 Suitable bases are, for example, alkali metal hydroxides, such as sodium hydroxide or potassium hydroxide, or alkali metal carbonates, such as caesium carbonate, sodium carbonate or potassium carbonate, or amides, such as lithium diisopropylamide, or other bases, such as DBU, triethylamine or diisopropylethylamine; preference is given to diisopropylethylamine or triethylamine.

20 In process step A (if X^1 represents hydroxyl) and in process B, the reaction of compound (II) with compound (III) and of compound (XI) with compound (VI), respectively, to give compounds of the formula (I) are carried out in inert solvents, in the presence of customary condensing agents, if appropriate in the presence of a base, 25 preferably in a temperature range of from room temperature to 50°C at atmospheric pressure.

30 Suitable inert solvents are, for example, halogenated hydrocarbons, such as methylene chloride, trichloromethane, carbon tetrachloride, trichloroethane, tetrachloroethane, 1,2-dichloroethane or trichloroethylene, ethers, such as diethyl ether, methyl tert-butyl ether, dioxane, tetrahydrofuran, glycol dimethyl ether or diethylene

glycol dimethyl ether, hydrocarbons, such as benzene, xylene, toluene, hexane, cyclohexane or mineral oil fractions, or other solvents, such as nitromethane, ethyl acetate, acetone, dimethylformamide, dimethylacetamide, 1,2-dimethoxyethane, dimethyl sulphoxide, acetonitrile or pyridine; preference is given to tetrahydrofuran,
5 dimethylformamide, 1,2-dichloroethane or methylene chloride.

Customary condensing agents are, for example, carbodiimides, such as, for example, N,N'-diethyl-, N,N'-dipropyl-, N,N'-diisopropyl-, N,N'-dicyclohexylcarbodiimide, N-(3-dimethylaminoisopropyl)-N'-ethylcarbodiimide hydrochloride (EDC), N-cyclo-
10 hexylcarbodiimide-N'-propyloxymethyl polystyrene (PS-carbodiimide) or carbonyl compounds, such as carbonyldiimidazole, or 1,2-oxazolium compounds, such as 2-ethyl-5-phenyl-1,2-oxazolium 3-sulphate or 2-tert-butyl-5-methylisoxazolium perchlorate, or acylamino compounds, such as 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline, or propanephosphonic anhydride, or isobutyl chloroformate, or bis-(2-oxo-
15 3-oxazolidinyl)phosphoryl chloride or benzotriazolyloxytri(dimethylamino)phosphonium hexafluorophosphate, or O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU), 2-(2-oxo-1-(2H)-pyridyl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TPTU) or O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU), or 1-hydroxybenzotriazole (HOBt), or
20 benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP), or mixtures of these.

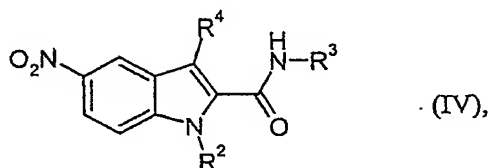
Suitable bases are, for example, alkali metal carbonates, such as, for example, sodium carbonate or potassium carbonate or sodium bicarbonate or potassium
25 bicarbonate, or organic bases, such as trialkylamines, for example triethylamine, N-methylmorpholine, N-methylpiperidine, 4-dimethylaminopyridine or diisopropylethylamine.

Preference is given to the combination of N-(3-dimethylaminoisopropyl)-N'-ethylcarbodiimide hydrochloride (EDC), 1-hydroxybenzotriazole (HOBt) and triethyl-
30 amine; O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophos-

- 20 -

phate (HATU) and triethylamine or N-(3-dimethylaminoisopropyl)-N'-ethylcarbodiimide hydrochloride (EDC) and 4-dimethylaminopyridine in dimethylformamide or carbonyldiimidazole in 1,2-dichloroethane.

5 To prepare compounds of the formula (II) for [A], compounds of the formula (IV)



in which

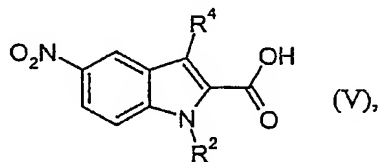
10 R^2 , R^3 and R^4 are as defined above,

are reacted with reducing agents in inert solvents.

Compounds of the formula (IV) can be prepared by two different routes.

15

[A 1] Firstly, compounds of the formula (V)



in which

20

R^2 and R^4 are as defined above,

are reacted either with compounds of the formula (VI)

- 21 -



in which

R^3 is as defined above,

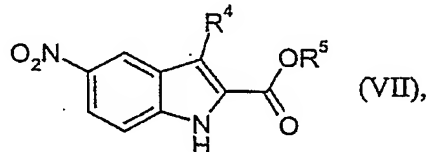
5

under the reaction conditions described for the reaction of compounds of the formula (II) with compounds of the formula (III) to give compounds of the formula (I) (if X^1 represents hydroxyl),

10 or compounds of the formula (V) are initially reacted with thionyl chloride and then with compounds of the formula (VI), in inert solvents, if appropriate in the presence of a base.

To prepare the compounds of the formula (V), compounds of the formula (VII)

15



in which

R^4 is as defined above and

20

R^5 represents alkyl, preferably methyl or ethyl,

are reacted, in a one-step or two-step process, with compounds of the formula (VIII)

25



in which

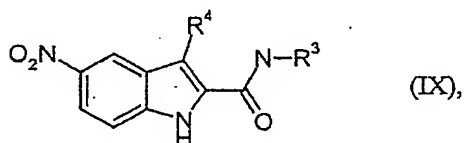
R^2 is as defined above and

- 22 -

X^2 represents halogen, preferably bromine or chlorine,

in the presence of a base, in inert solvents. In the two-step process, in the first step,
5 the indole nitrogen atom is alkylated and, in a second step, after a change of base, the
ester is hydrolysed to the acid.

[A 2] It is also possible to prepare compounds of the formula (IV) by reacting
10 compounds of the formula (IX)



in which

R^3 and R^4 are as defined above,

15

with compounds of the formula (VIII)



in which

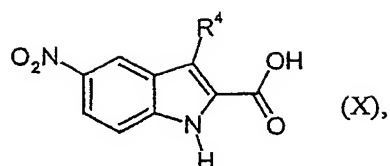
20

R^2 and X^2 are as defined above,

in the presence of a base, in inert solvents.

25 To prepare compounds of the formula (IX), compounds of the formula (X)

- 23 -



in which

R^4 is as defined above,

5

are reacted either with compounds of the formula (VI)



in which

10

R^3 is as defined above,

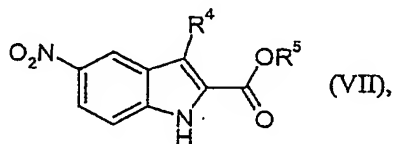
under the reaction conditions described for the reaction of compounds of the formula (II) with compounds of the formula (III) to give compounds of the formula (I) (if X^1 represents hydroxyl),

15

or compounds of the formula (X) are initially reacted with thionyl chloride and then with compounds of the formula (VI) in inert solvents, if appropriate in the presence of a base.

20

To prepare the compounds of the formula (X), the ester function of compounds of the formula (VII)



25

in which

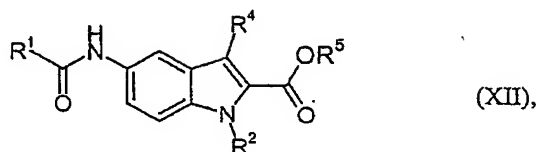
- 24 -

R^4 and R^5 are as defined above,

is hydrolysed.

5

To prepare the compounds of the formula (XI) for [B], the ester function of compounds of the formula (XII)



10 in which

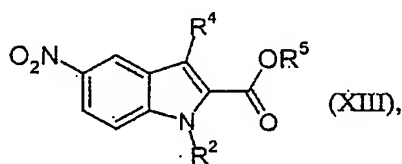
R^1 , R^2 , R^4 and R^5 are as defined above,

is hydrolysed.

15

Compounds of the formula (XII) can be prepared by two different routes.

[B 1] Firstly, the nitro group in compounds of the formula (XIII)



20

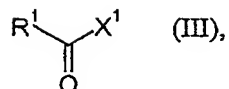
in which

R^2 , R^4 and R^5 are as defined above

25

is reduced and the product is then reacted with compounds of the formula (III)

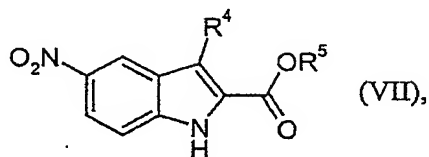
- 25 -



in which

5 R^1 and X^1 are as defined above.

To prepare compounds of the formula (XIII), compounds of the formula (VII)



10 in which

R^4 and R^5 are as defined above

are reacted with compounds of the formula (VIII)

15



in which

R^2 and X^2 are as defined above

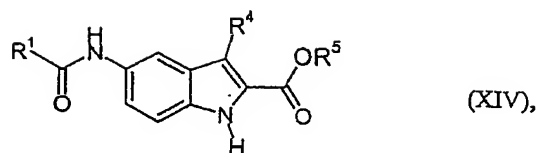
20

in the presence of a base in inert solvents.

[B 2] It is also possible to prepare compounds of the formula (XII) by reacting
compounds of the formula (XIV)

25

- 26 -



in which

R¹, R⁴ and R⁵ are as defined above

5

with compounds of the formula (VIII)



in which

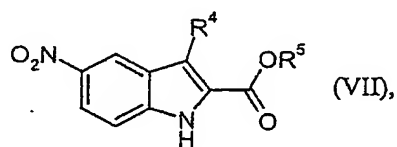
10

R² and x² are as defined above,

in the presence of a base in inert solvents.

15

To prepare compounds of the formula (XIV), the nitro group in compounds of the formula (VII)



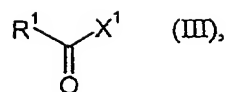
in which

20

R⁴ and R⁵ are as defined above

is reduced, and the product is then reacted with compounds of the formula (III)

- 27 -



in which

R^1 and X^1 are as defined above.

5

Suitable inert solvents are, for example, halogenated hydrocarbons, such as methylene chloride, trichloromethane, carbon tetrachloride, trichloroethane, tetrachloroethane, 1,2-dichloroethane or trichloroethylene, ethers, such as diethyl ether, methyl tert-butyl ether, dioxane, tetrahydrofuran, glycol dimethyl ether or diethylene glycol dimethyl ether, alcohols, such as methanol, ethanol, propanol, isopropanol or butanol, hydrocarbons, such as benzene, xylene, toluene, hexane, cyclohexane or mineral oil fractions, or other solvents, such as nitromethane, ethyl acetate, acetone, dimethylformamide, dimethylacetamide, 1,2-dimethoxyethane, dimethyl sulphoxide, acetonitrile or pyridine.

15

Suitable bases are the customary inorganic or organic bases. These preferably include alkali metal and alkaline earth metal hydroxides, such as, for example, lithium hydroxide, sodium hydroxide or potassium hydroxide, or alkali metal and alkaline earth metal carbonates, such as caesium carbonate, sodium carbonate or potassium carbonate, or sodium methoxide or potassium methoxide or sodium ethoxide or potassium ethoxide or potassium tert-butoxide, or amides, such as sodium amide, lithium bis(trimethylsilyl)amide or lithium diisopropylamide, or organometallic compounds, such as butyllithium or phenyllithium, or amines, such as triethylamine, diisopropylethylamine, diisopropylamine, N-methylmorpholine, 4-dimethylaminopyridine or pyridine, or other bases such as sodium hydride or DBU. If appropriate, in addition to the bases, additives such as crown ethers (for example 18-crown-6), or inorganic salts, such as, for example, sodium iodide or copper(I) bromide are employed.

25

Suitable reducing agents are, for example, tin dichloride, titanium trichloride or palladium on activated carbon and hydrogen, where palladium on activated carbon is, if appropriate, employed with added ammonium acetate and/or acetic acid.

5 The reaction step (IV) \rightarrow (II) and the first step (reduction) in reaction steps (XIII) + (III) \rightarrow (XII) and (VII) + (III) \rightarrow (XIV) is preferably carried out using tin dichloride in ethanol, methanol or dimethylformamide or using palladium on carbon in the presence of ammonium formate in ethyl acetate/ethanol, preferably in a temperature range of from room temperature to the reflux temperature of the solvents, at from
10 atmospheric pressure to 3 bar.

The first step of reaction steps (V) + (VI) \rightarrow (IV) and (X) + (VI) \rightarrow (IX) is preferably carried out using an excess of thionyl chloride as solvent, preferably in a temperature range of from 50°C to the reflux temperature of the reactants at atmospheric pressure.

15 In the second step, the reaction is preferably carried out in methylene chloride using the base triethylamine, preferably in a temperature range of from 0°C to 40°C at atmospheric pressure.

In the one-step process, the reaction step (VII) + (VIII) \rightarrow (V) is preferably carried
20 out in dimethyl sulphoxide using the base potassium hydroxide or sodium hydroxide, preferably in a temperature range of from 0°C to 40°C at atmospheric pressure.

The alkylation in the first step of the two-step process and in reaction steps (XI) + (VIII) \rightarrow (IV); (VII) + (VIII) \rightarrow (XIII); (XIV) + (VIII) \rightarrow (XII) is preferably carried
25 out in dimethyl sulphoxide using the base sodium hydride or in THF using the base potassium tert-butoxide and with addition of crown ether, preferably in a temperature range of from room temperature to 50°C at atmospheric pressure. If R² in the compounds (VIII) represents an aromatic radical, the reaction (VII) + (VIII) \rightarrow (XIII) is carried out in the presence of the base potassium carbonate, with added copper(I)
30 bromide.

The hydrolysis in the second step of reaction step (VII) + (VIII) \rightarrow (V) is preferably carried out in dimethyl sulphoxide using the base potassium hydroxide or sodium hydroxide, preferably in a temperature range of from 0°C to 40°C at atmospheric pressure.

5

The reaction steps (VII) \rightarrow (X) and (XII) \rightarrow (XI) are preferably carried out in methanol and THF using, as base, aqueous lithium hydroxide solution, preferably in a temperature range of from RT to 90°C at atmospheric pressure.

10 The second step (acylation) in reaction steps (XIII) + (III) \rightarrow (XII) and (VII) + (III) \rightarrow (XIV) is preferably carried out in the solvent dichloromethane or THF in the presence of the base triethylamine in a temperature range of from 0°C to 40°C at atmospheric pressure.

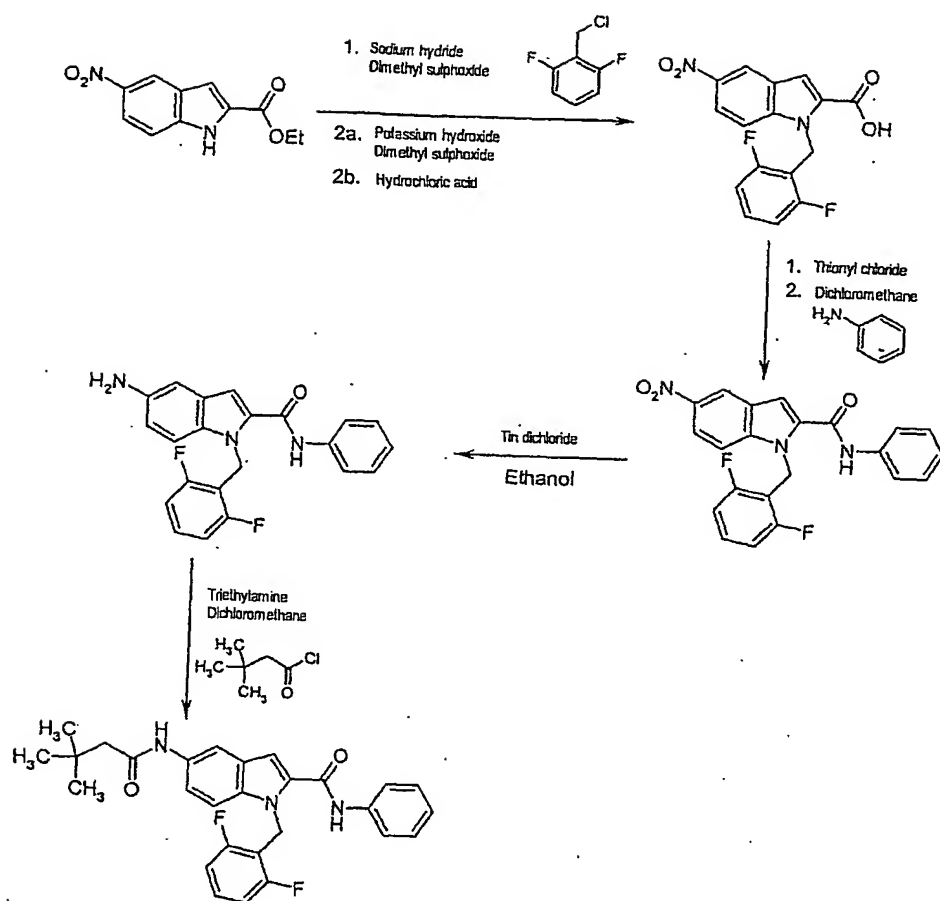
15 The compounds of the formulae (III), (VI) and (VIII) are known per se to the person skilled in the art or can be prepared by customary processes known from the literature.

20 The compounds of the formula (VII) are known per se to the person skilled in the art or can be prepared by customary processes known from the literature (cf.: A. Guy, J.-P. Guetté, *Synthesis* 1980, 222-223).

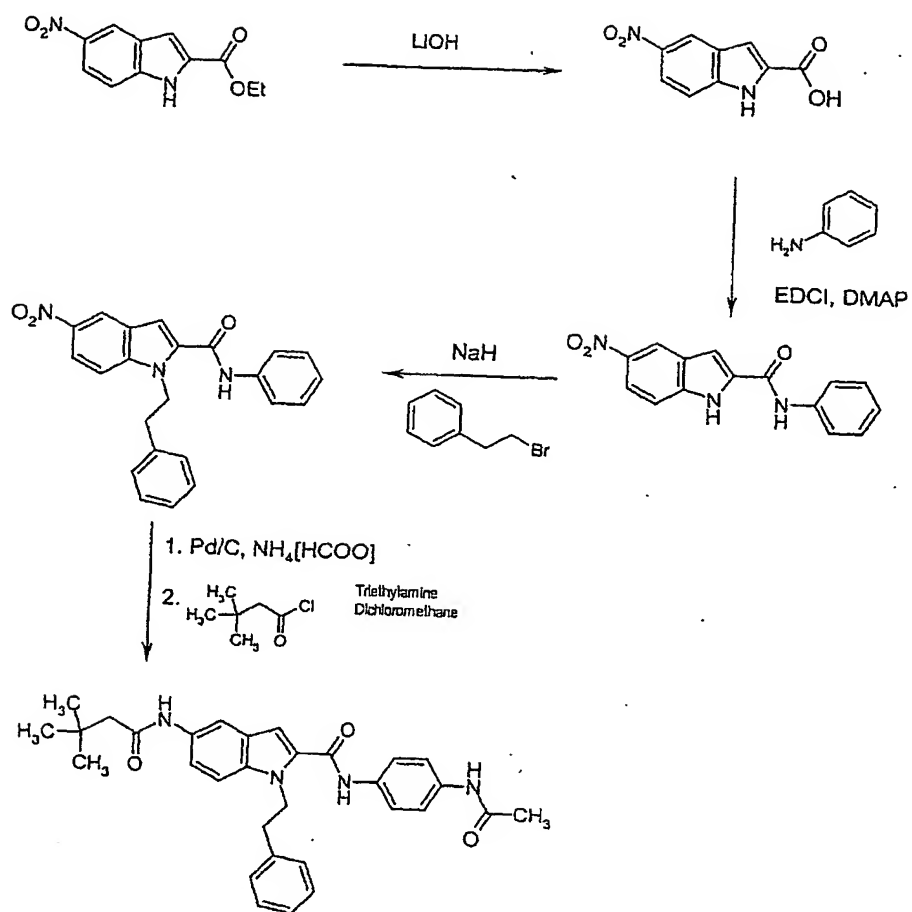
The processes described above can be illustrated in an exemplary manner by the formula schemes below:

25

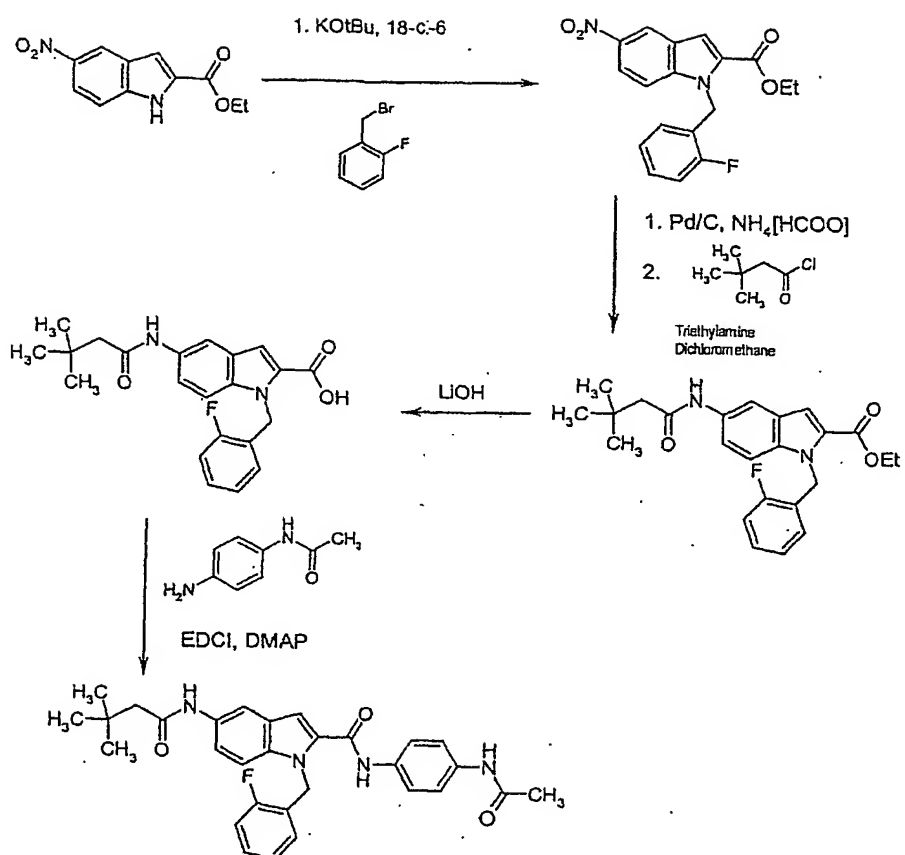
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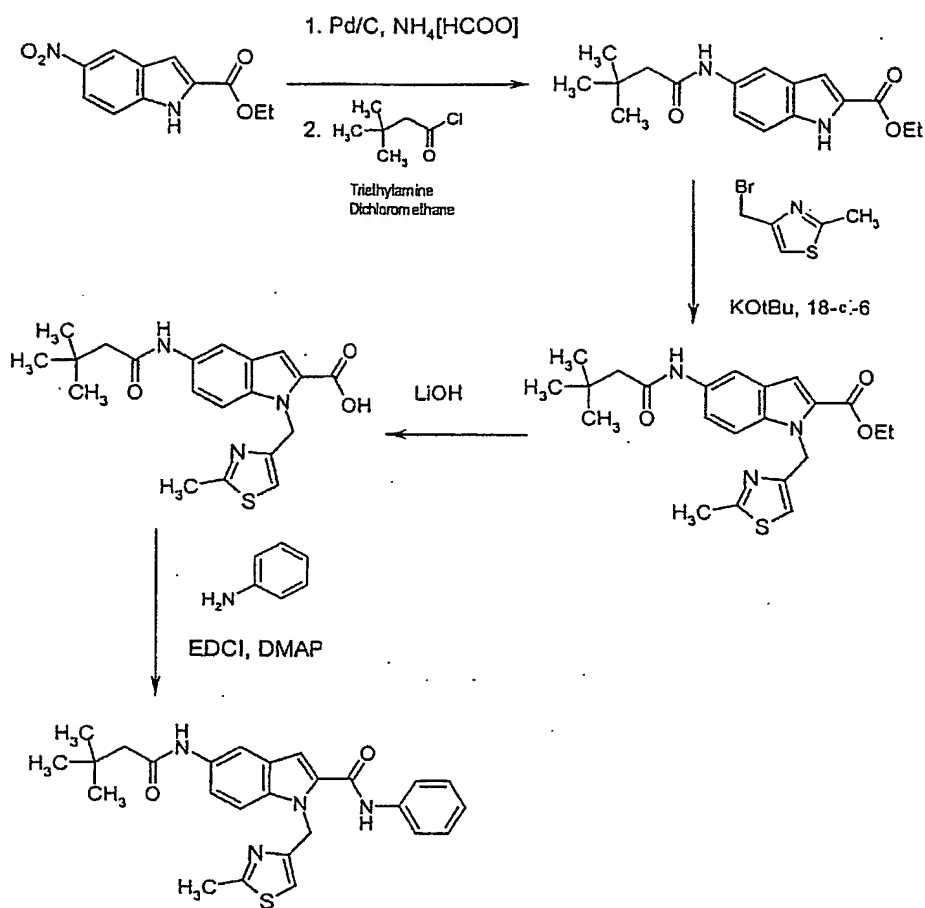
- 31 -



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The compounds which act as ECE inhibitors and the compounds of the formula (I) have an unforeseeable useful spectrum of pharmacological activity and are therefore suitable in particular for the prophylaxis and/or treatment of disorders in humans and animals, in particular disorders which are caused on defects in the bET/ET conversion.

The pharmaceutical activity of the compounds of the formula (I) can be explained by their action as ECE inhibitors.

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Owing to their pharmacological properties, the compounds with ECE inhibitory activity, in particular the compounds of the formula (I) can be used on their own or in combination with one or more other active compounds for the prophylaxis and/or treatment of disorders in human and veterinary medicine, in particular of urological disorders such as benign prostatic hyperplasia and overactive bladder .

The present invention relates to the use of the compounds of the formula (I) for preparing medicaments for the treatment of the syndromes mentioned above.

The present invention furthermore provides medicaments comprising at least one compound of the formula (I), preferably together with one or more pharmacologically acceptable auxiliaries or carriers, and their use for the purposes mentioned above.

The active compounds can act systemically and/or locally. For this purpose, they can be administered in a suitable manner, such as, for example, orally, parenterally, pulmonarily, nasally, sublingually, lingually, buccally, rectally, transdermally, conjunctivally, otically, as stents or as an implant.

For these administration routes, the active compounds can be administered in suitable administration forms, oral administration being preferred.

For oral administration, known administration forms delivering the active compound rapidly and/or in modified form, such as, for example, tablets (uncoated and coated tablets, for example tablets provided with enteric coatings or film-coated tablets), capsules, sugar-coated tablets, granules, pellets, powders, emulsions, suspensions and solutions, are suitable.

Parenteral administration can be carried out with avoidance of an absorption step (intravenous, intra-arterial, intracardiac, intraspinal or intralumbal) or with involvement of an absorption (intramuscular, subcutaneous, intracutaneous, percutaneous, or

intraperitoneal). Suitable administration forms for parenteral administration are, inter alia, injection and infusion preparations in the form of solutions, suspensions, emulsions, lyophilisates and sterile powders.

5 For the other administration routes, for example, pharmaceutical forms for inhalation (inter alia powder inhalers, nebulizers), nasal drops/solutions, sprays; tablets or capsules to be administered lingually, sublingually or buccally or capsules, suppositories, aural and ophthalmic preparations, vaginal capsules, aqueous suspensions (lotions, shake mixtures), lipophilic suspensions, ointments, creams, milk, pastes,
10 dusting powders or implants are suitable.

The active compounds can be converted in a manner known per se into the application forms mentioned. This is carried out using inert non-toxic, pharmaceutically suitable excipients. These include, inter alia, vehicles (for example microcrystalline
15 cellulose), solvents (for example liquid polyethylene glycols), emulsifiers (for example sodium dodecyl sulphate), dispersing agents (for example polyvinylpyrrolidone), synthetic and natural biopolymers (for example albumin), stabilizers (for example antioxidants such as ascorbic acid), colorants (for example inorganic pigments such as iron oxides) or taste and/or odour corrigents.

20 In general, it has proved advantageous to administer amounts of approximately 0.001 to 50 mg/kg, preferably approximately 1 to 50 mg/kg, of body weight, in the case of oral administration approximately 0.01 to 25 mg/kg, preferably approximately 0.5 to 5 mg/kg, of body weight, to achieve effective results.

25 In spite of this, it may be necessary to depart from the amounts mentioned, namely depending on the body weight or the type of administration route, on the individual response towards the medicament, the manner of its formulation and the time or interval at which administration takes place. Thus, in some cases it may be sufficient
30 to manage with less than the abovementioned minimum amount, while in other cases the upper limit mentioned has to be exceeded. In the case of administration of

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relatively large amounts, it may be advisable to divide these into a number of individual doses over the course of the day.

The present invention is illustrated using the non-limiting preferred examples below;
5 however, the invention is not in any way restricted by these examples.

Unless indicated otherwise, the percentages in the examples below are in each case based on weight; parts are parts by weight.

Evaluation of the physiological activity

To examine the *in vitro* action of the compounds according to the invention, the following biological assays may be used:

5

Functional *in vitro* assay

The ECE activity for identifying the substances described herein originates from the endothelial cell line EA.hy926. The ECE-inhibitory action of the compounds in this invention is tested as described below:

10

For 12 – 48 h, EA.hy296 cells are cultivated in a 384-well cell culture dish in 80 µl of cell culture medium (DMEM supplemented with 10% FCS, 2 mM glutamine, 10 mM HEPES, 1 mM sodium pyruvate and 1× HAT (Gibco 21060-017)) in a humid atmosphere (100% atmospheric humidity) enriched with 7% v/v of CO₂ at 37°C. After confluence has been reached, and immediately prior to the actual beginning of measurement, the supernatant of the cell culture is pipetted off and replaced by 40 or 80 µl of the same medium to which 1-100 nM bET has been added. After 30 – 120 minutes under otherwise identical cell culture conditions, the supernatant is pipetted off. Cellular components are removed by centrifugation in a customary bench-top centrifuge (10 000 rpm; 2 minutes). The resulting clear supernatant is either used directly as described below or shock-frozen in dry ice and then stored at –20°C. Directly removed supernatant or thawed, stored supernatant are measured in an enzyme immunoassay (EIA).

15

20

25

To determine the inhibitory activity of ECE inhibitors, EA.hy296 cells are incubated with the test substance in a concentration between 0.001-5 µM under the conditions described above. To minimize possible interference by neutral endopeptidase (NEP24.11), 100 µM of thiophane are added during the bET incubation of the EA.hy926 cells.

30

- 38 -

The proportion of the ET-1 formed by ECE cleavage is measured as follows: depending on the amount of converted bET, the samples are, prior to use, diluted 2 – 100-fold with EIA. An appropriate dilution of the cell supernatant is incubated in 100 µl portions for 14-18 hours in the sample tubes of the EIA kit Biomedica B1-20052.

The experimental data are compiled in the Table 1 below.

Table 1

Example No.	IC ₅₀ (µM)
7	1
57	1.5
58	1.6
60	0.7
62	0.7

***In vivo* assay**

Cystometry study in bladder outlet obstruction (BOO) model in rats

(1) Animals

Thirty-five female Sprague-Dawley rats (average weight 227 ± 2 g) were used for the study. They were housed under a 12 hours light/dark photocycle, food and water were provided ad libitum. The animals were divided in 3 groups: Animals with BOO received the ECE-inhibitor (group A), Animals with BOO received only the vehicle (group B), Animals without BOO received the ECE-inhibitor (group C).

(2) Surgical procedure and administration of ECE inhibitor

5 The rats in the BOO group were anesthetized with a mixture of ketamine (Ketalar®, Parke Davis, Barcelona, Spain; 765 mg/kg IP) and xylazine (Rompun®, Bayer, Leverkusen, Germany, 15 mg/kg IP). The abdomen was opened by a lower midline incision, bladder and urethra were identified, and freed from surrounding tissues. Bladder and the urethrovesical junction were exposed through a lower abdominal midline incision, and the surrounding fat tissue was removed. A 0.9 mm metal rod was placed alongside the proximal
10 urethra and a 3-0 silk ligature was tied tightly around the urethra and the rod, which was consequently removed. The abdomen was then closed anatomically.

15 Beginning the day after creation of the obstruction, the animals in the treatment group and the sham-operated animals were treated with the ECE inhibitor (50mg/kg) by oral gavage once a day at noon. The drug was prepared daily, 30 minutes prior to medication (see below).

20 In the afternoon of day 13 after the obstruction the abdominal suture was reopened and the bladder was exposed. Through a mini-incision in the bladder dome a polyethylene catheter (PE 50) with a small cuff was inserted and secured with a purestring suture (5-0 silk). The obstructing ligature was removed. The catheter was tunneled subcutaneously and led out through a small insertion on the back of the neck. The bladder was then put back into
25 the anatomical position and the abdomen was closed.

30 Sham operated animals received surgery following a similar protocol, without the last step of tying the obstruction. Unoperated animals served as controls and received a bladder catheter as described above, 1 days prior to cystometry.

- 40 -

(3) Cystometry study

The following morning after insertion of the catheter, 14 days after creation of the obstruction, the cystometric investigation was performed without any anesthesia or restraint. The rats were placed into a metabolic cage (Gazzada, Buguggiatade, Italy), which allowed the measurement of the amount of voided urine by means of a fluid collector, connected to a force displacement transducer (FT 03 D; Grass instrument Co., MA, USA). The bladder catheter was connected to a pressure transducer, which in turn was connected to a Grass® 7E Polygraph recorder. The bladder was continuously filled with saline at room temperature by means of a microinjector pump (CMA 100, Carnegie Medicine, Solna, Sweden), at a filling speed of 160 μ l/min. After a stabilization period of 30–60 minutes, in which the bladder was continuously filled, reproducible voiding patterns were achieved and recorded over a period of 30 minutes. The animals were continuously observed in order to distinguish between moving artifacts and non-voiding bladder contractions. The amount of residual urine was investigated at the end of the cystometry, after reproducible micturition patterns were recorded. Directly after micturition the catheter was detached and the residual urine was drained by carefully lowering of the catheter tip under bladder level. This procedure was repeated 3 times and the drained volume measured by means of a micro syringe. Based on this information the functional and anatomical capacity was calculated. The functional capacity equals the amount of saline infused into the bladder between 2 voids, to calculate the anatomical capacity the average amount of residual urine was added to the functional capacity.

Right after the cystometry the animals were medicated again, 2 hours later they were killed by CO₂-asphyxia. The catheter position was confirmed and the bladder checked for abnormalities as stones or signs of infection. Bladder, urethra and the proximal ureters were removed en bloc and transferred into ice-cold Krebs solution. The bladders were weighed.

(4) Drugs and drug-preparation

Solutol® was warmed to 37°C. The ECE inhibitor was crushed with a mortar and mixed with ethanol. The warmed Solutol® was added, and after the compounds were dissolved, the water was added. The ratio of the carrier substances was 10% Ethanol, 40% Solutol, 50% Water. The drug was administered at a dose of 50 mg/kg/d, the vehicle group received the Ethanol/Solutol/water mixture in amounts according to the treatment group.

Normal Krebs solution was composed as following (mM): NaCl 119, KCl 4.6, CaCl₂ 1.5, MgCl₂ 1.2, NaHCO₃ 15, NaH₂PO₄ 1.2, and glucose 11.

(5) Analysis of data

All values are reported as the mean \pm SEM. Statistical significance was determined by Student's t-test and Bonferroni correction as appropriate. $P < 0.05$ was required for statistical significance.

In vivo profile of ECE inhibitors

An increase in bladder weight was observed in both the ECE-treated group and the vehicle-treated group, compared to the sham, however the increase was not significant in the ECE-treated group. The basal bladder pressure, as well as the threshold pressure, were unchanged in all groups, though slightly increased in both obstructed groups.

Micturition interval was significantly increased in the ECE-treated group and greatly in the vehicle treated animals, while the micturition volume was significantly increased in both obstructed groups. Functional and anatomical capacity was significantly increased in the ECE-treated group, and enhanced in the vehicle group.

Although significant decrease in micturition pressure was seen in the vehicle-treated group, no change in micturition pressure was observed in ECE-treated group, compared to the sham.

5

No development of residual urine was observed in the ECE-treated group, while some in vehicle-treated group showed such development (4 out of 11 animals). (Fig. 1, Table 2).

10

Spontaneous, non-voiding bladder contractions, which were not seen in the sham group, occurred in 9 out of 11 vehicle treated, but they were observed in only 3 out of 8 ECE-treated animals. The amplitude of these contractions mounted to over 15 cm/H₂O in the vehicle group, sometimes higher than the actual micturition pressure, while then remained below 5 cm/H₂O in the ECE-treated animals (Fig. 2).

15

The voiding contractions in the sham group were rapidly developed and short lasted. They were slightly prolonged in the ECE-treated group, but lasted for up to 30 seconds in the vehicle-treated group. (Table 2, Fig. 3)

20

In men with BPH, increases of micturition volume, micturition interval and both functional and anatomical capacity in voiding patterns are commonly observed. All these changes were observed in BOO rats in present study, indicating relevancy of present BOO model to BPH.

25

The chronic and oral treatment of ECE inhibitor in BOO rats significantly changed the voiding patterns. Namely, the micturition pressure was increased to the level of sham, and micturition duration was also decreased. One of symptoms in BPH patients is known as obstructive symptom during urine voiding. Therefore, increase of micturition pressure and decrease of micturition duration by ECE inhibitor should

30

be beneficial for BPH patients.

Also, spontaneous non-voiding contractions observed in BOO rats are regarded as the irritative symptom in men with BPH and overactive bladder. These non-voiding contractions were inhibited by the treatment with ECE inhibitor. Therefore, these obtained results indicate the therapeutic potential of ECE inhibitor for the treatment of men with BPH and overactive bladder.

Table 2

	sham (n = 4)	Vehicle (n = 11)	ECE inhibitor (n = 8)
Bladder weight (mg)	134.0 ± 8.3	395.4 ± 40.8 *	336.0 ± 50.2
MI (min)	2.7 ± 0.4	4.9 ± 0.8	5.8 ± 0.4 *
MP (cm H ₂ O)	86.8 ± 3.5	33.0 ± 5.9*	68.4 ± 9.4
TP (cm H ₂ O)	4.0 ± 1.0	11.0 ± 3.0	10.0 ± 2.0
BP (cm H ₂ O)	2.0 ± 0.0	7.0 ± 2.0	8.0 ± 2.0
MV (ml)	0.45 ± 0.06	0.83 ± 0.08*	0.89 ± 0.07*
RU (ml)	0.0	0.05 ± 0.03	0.0
FC (ml)	0.42 ± 0.06	0.71 ± 0.09	0.92 ± 0.06*
AC (ml)	0.42 ± 0.06	0.76 ± 0.10	0.92 ± 0.06*
MD (sec)	2.0 ± 0.0	15.0 ± 3.0	3.0 ± 1.0

(Values represent mean ± SEM, * p< 0.05 vs. sham, + p< 0.05 vs. vehicle

MI micturition interval; MP micturition pressure; TP threshold pressure; BP basal pressure; MV micturition volume; RU residual urine; FC functional capacity; AC anatomical capacity; MD micturition duration.).

15 BRIEF DESCRIPTION OF DRAWINGS

Fig. 1 presents graphs which show the bladder weight (BW), micturition pressure (MP) and micturition duration (MD) in sham-operated rats (sham), BOO rats

treated with vehicle (vehicle) and BOO rats treated with ECE inhibitor (treatment).

5 Fig. 2 presents graphs which show the amplitude and frequency of the non-voiding contractions in sham-operated rats (sham), BOO rats treated with vehicle (vehicle) and BOO rats treated with ECE inhibitor (treatment).

10 Fig. 3 presents charts showing cystometogram in sham-operated rats (sham), BOO rats treated with vehicle (vehicle) and BOO rats treated with ECE inhibitor (treatment).

Examples**Abbreviations:**

5	aq.	aqueous
	CDCl ₃	deuteriochloroform
	CH	cyclohexane
	DCI	direct chemical ionization (in MS)
	DCM	dichloromethane
10	DMAP	4-dimethylaminopyridine
	DMF	dimethylformamide
	DMSO	dimethyl sulphoxide
	EDC	N-(3-dimethylaminoisopropyl)-N'-ethylcarbodiimide hydrochloride
15	EA	ethyl acetate (acetic acid ethyl ester)
	EI	electron-impact ionization (in MS)
	eq	equivalent(s)
	ESI	electrospray ionization (in MS)
	m.p.	melting point
20	sat.	saturated
	h	hour
	HATU	O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
	HPLC	high-pressure, high-performance liquid chromatography
25	LC-MS	liquid-chromatograph-coupled mass spectroscopy
	lit.	literature (reference)
	sol.	solution
	MW	molecular weight
	ml	millilitre
30	MS	mass spectroscopy
	NMR	nuclear magnetic resonance

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	o	ortho
	p	para
	p.a.	pro analysi
	prep.	preparative
5	RF	reflux
	RP	reverse phase (in HPLC)
	RT	room temperature
	R _t	retention time (in HPLC)
	THF	tetrahydrofuran
10	dil.	dilute
	cf.	compare
	vol.	volume
	decomp.	decomposition

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LC/MS and HPLC methods:MHZ2Q = method 4

5	MS unit:	Micromass Quattro LCZ			
	Ionization:	ESI positive/negative			
	HPLC unit:	HP 1100			
	UV detector DAD:	208-400 nm			
	Oven temp.:	40°C			
10	Column:	Symmetry C 18			
		50 mm × 2.1 mm	3.5 µm		
15	Gradient	Time (min)	A:%	B:%	Flow rate (ml/min)
		0.00	10.0	90.0	0.50
		4.00	90.0	10.0	0.50
		6.00	90.0	10.0	0.50
		6.10	10.0	90.0	1.00
		7.50	10.0	90.0	0.50
	A:	acetonitrile + 0.1% formic acid			
20	B:	water + 0.1% formic acid			

Method 1 (LCMS) = Method MHZ2P01

Instrument: Micromass Platform LCZ, HP1100; column: symmetry C18, 50 mm ×
 25 2.1 mm, 3.5 µm; eluent A: water + 0.05% formic acid, eluent B: acetonitrile + 0.05%
 formic acid; gradient: 0.0 min 90% A → 4.0 min 10% A → 6.0 min 10% A; oven:
 40°C; flow rate: 0.5 ml/min; UV detection: 208-400 nm.

Method 2 (LCMS) = Method SMKL-ZQ-2

Instrument: Waters Alliance 2790 LC; column: symmetry C18, 50 mm × 2.1 mm, 3.5 µm; eluent A: water + 0.1% formic acid, eluent B: acetonitrile + 0.1% formic acid; gradient: 0.0 min 5% B → 5.0 min 10% B → 6.0 min 10% B; temperature: 50°C; flow rate: 1.0 ml/min; UV detection: 210 nm.

Method 3 (LCMS) = Method SMKL 03042001- acid - 210

Instrument: Finnigan MAT 900S, TSP: P4000,AS3000,UV3000HR; column: symmetry C18, 150 mm × 2.1 mm, 5.0 µm; eluent C: water, eluent B: water + 0.3 g 35% strength HCl, eluent A: acetonitrile; gradient: 0.0 min 2% A → 2.5 min 95% A → 5 min 95% A; oven: 70°C; flow rate: 1.2 ml/min; UV detection: 210 nm.

Method 4 (LCMS) = Method MHZ2Q**Method 5 (LCMS) = Method SMKL ZQ-5-CS**

MS unit: Micromass ZQ; HPLC unit: Waters Alliance 2790; column: symmetry C18, 50 mm × 2.1 mm, 3.5 µm; eluent B: acetonitrile + 0.05% formic acid, eluent A: water + 0.05% formic acid; gradient: 0.0 min 10% B → 3.5 min 90% B → 5.5 min 90% B; oven: 50°C; flow rate: 0.8 ml/min; UV detection: 210 nm.

Method 6 (HPLC) = Method SYA-HPPSK2

Instrument: HP 1100 with DAD detection; column: Kromasil RP-18, 60 mm × 2 mm, 3.5 µm; eluent: A = 5 ml HClO₄/l H₂O, B = ACN; gradient: 0 min 2% B, 0.5 min 2% B, 4.5 min 90% B, 6.5 min 90% B; flow rate: 0.75 ml/min; temp.: 0°C; detection UV 210 nm.

Method 7 (HPLC) = Method SMKL-N1-1-Low Vol ACN-HCl-210.met

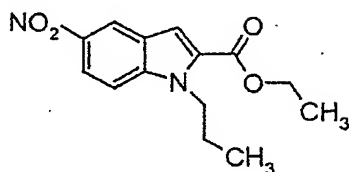
Instrument: 1 column: symmetry C18 2.1 × 150 mm; eluent: A = ACN, B = 0.6 g
30% strength HCl/water; gradient: 0 min 10% A flow rate 0.60 ml/min, 4 min 90% A
5 flow rate 0.60 ml/min, 9 min 90% A flow rate 0.80 ml/min; temp.: 50°C; UV
detection 210 nm.

Starting materials

Example I

Ethyl 5-nitro-1-propyl-1H-indole-2-carboxylate

5



Under argon, 937 mg (4.00 mmol) of ethyl 5-nitro-1H-indole-2-carboxylate (A. Guy, J.-P. Guetté, *Synthesis* 1980, 222-223) are initially charged in 12 ml of dimethyl sulphoxide. 4.40 mmol of sodium hydride (176 mg of a 60% dispersion in paraffin) are added a little at a time, and the mixture is stirred at 50°C for 30 min. After cooling to RT, 170 mg (4.40 mmol) of propyl iodide are added, and the mixture is stirred at RT for another 3 h. The reaction mixture is poured into 30 ml of water and extracted with ethyl acetate (6 × 30 ml). The combined organic phases are washed with 50 ml of sat. sodium chloride sol., dried over sodium sulphate and freed from the solvent using a rotary evaporator. The resulting brown crude product is purified by column chromatography (silica gel 60, mobile phase gradient cyclohexane → cyclohexane-ethyl acetate 3:1), giving the product as second fraction.

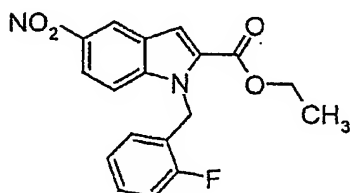
Yield: 958 mg (3.48 mmol, 77% of theory).

MS (DCI): $m/z = 294$ ($M + NH_4$)⁺.

¹H-NMR (500 MHz, DMSO-d₆): $\delta = 8.76$ (d, 1H), 8.17 (dd, 1H), 7.89 (d, 1H), 7.58 (s, 1H), 4.60 (dd, 2H), 4.36 (q, 2H), 1.74 (sextet, 2H), 1.35 (t, 3H), 0.84 (t, 3H).

Example II

Ethyl 1-(2-fluorobenzyl)-5-nitro-1H-indole-2-carboxylate



5

The preparation is carried out as described for Example I using 940 mg (4.00 mmol) of ethyl 5-nitro-1H-indole-2-carboxylate and 780 mg (4.15 mmol) of 2-fluorobenzyl bromide, reaction time 6 h.

Yield: 980 mg (72% of theory).

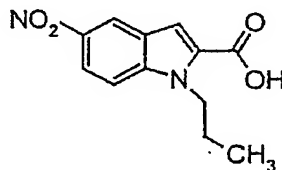
10 MS (DCI): $m/z = 360$ ($M+NH_4$)⁺.

¹H-NMR (300 MHz, DMSO-d₆): $\delta = 8.80$ (d, 1H), 8.17 (dd, 1H), 7.82 (d, 1H), 7.68 (d, 1H), 7.35-7.18 (m, 2H), 7.03 (dt, 1H), 6.56 (dt, 1H), 5.98 (s, 2H), 4.29 (q, 2H), 1.27 (t, 3H).

15

Example III

5-Nitro-1-propyl-1H-indole-2-carboxylic acid



20

236 mg (3.68 mmol, 85% pure) of potassium hydroxide (powder) are initially charged in 10 ml of dimethyl sulphoxide, 961 mg (3.48 mmol) of the compound from Example I are added and the mixture is stirred at RT for half an hour. The reaction mixture is poured into about 100 ml of water and with cooling, 10% strength

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hydrochloric acid is added a little at a time to the solution until no more precipitate is formed. The precipitated solid is filtered off with suction and dried in a desiccator under reduced pressure overnight.

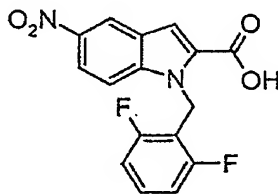
Yield: 812 mg (94% of theory)

5 m.p.: 197°C

¹H-NMR (300 MHz, DMSO-d₆): δ = 13.33 (br. s, 1H), 8.73 (d, 1H), 8.15 (dd, 1H), 7.85 (d, 1H), 7.53 (s, 1H), 4.61 (t, 2H), 1.74 (sextet, 2H), 0.83 (t, 3H).

Example IV

10 1-(2,6-Difluorobenzyl)-5-nitro-1H-indole-2-carboxylic acid



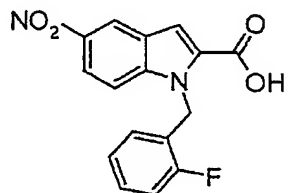
Under an atmosphere of argon, 5.49 g (83.2 mmol, 85% pure) of potassium
15 hydroxide (powder) are initially charged in 110 ml of dimethyl sulphoxide, 6.43 g (27.5 mmol) of ethyl 5-nitro-1H-indole-2-carboxylate (A. Guy, J.-P. Guetté, *Synthesis* 1980, 222-223) are added at RT and the mixture is stirred for 30 min. With ice-cooling, at an internal temperature of 5-10°C, 2,6-difluorobenzyl chloride (10.0 g, 61.5 mmol) is then added dropwise over a period of 15 min, and the mixture is stirred
20 at RT for 16 h. For work-up, the mixture is poured into 500 ml of water and acidified with dil. hydrochloric acid and the precipitated solid is filtered off with suction and pre-purified chromatographically on silica gel 60 (mobile phase gradient dichloromethane → dichloromethane-methanol 3:1). The resulting product is recrystallized from ethanol. This gives 4.33 g (47% of theory) of a pale-yellow crystalline solid.

25 MS (ESIpos): m/z = 333 (M+H)⁺.

¹H-NMR (300 MHz, DMSO-d₆): δ = 13.41 (br. s, 1H), 8.72 (d, 1H), 8.17 (dd, 1H), 7.71 (d, 1H), 7.54 (s, 1H), 7.37 (m, 1H), 7.05 (t and m, 2H), 6.07 (s, 2H).

Example V

1-(2-Fluorobenzyl)-5-nitro-1H-indole-2-carboxylic acid



5

Preparation analogously to Example III using 877 mg (2.56 mmol) of the compound from Example II. Yield: 732 mg (91% of theory)

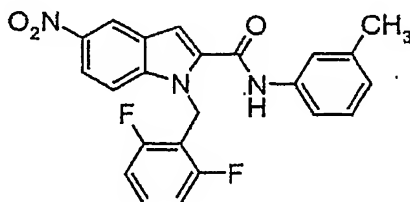
m.p.: 223°C

10 MS (DCI): $m/z = 332$ ($M+NH_4$)⁺.

¹H-NMR (500 MHz, DMSO-d₆): $\delta = 13.49$ (br. s, 1H), 8.79 (d, 1H), 8.15 (dd, 1H), 7.78 (d, 1H), 7.61 (s, 1H), 7.29 (m, 1H), 7.23 (m, 1H), 7.03 (t, 1H), 6.52 (t, 1H), 6.02 (s, 2H).

15 **Example VI**

1-(2,7-Difluorobenzyl)-N-(3-methylphenyl)-5-nitro-1H-indole-2-carboxamide



20 A little at a time, the compound from Example IV (1.40 g, 4.21 mmol) is introduced into 10 ml of thionyl chloride, and after the addition has ended, the mixture is stirred at the boil. After 60 min, the mixture is concentrated and the residue is mixed 3 times with about 50 ml of toluene each time and reconcentrated. The resulting indole-

- 54 -

carbonyl chloride is taken up in 50 ml of dichloromethane and, at 0°C, 2.94 ml (21.1 mmol) of triethylamine and then 587 mg (5.48 mmol) of 3-methylaniline are added. The mixture is stirred at room temperature for 16 h. The reaction solution is poured into 200 ml of water, the organic solvent is removed from the mixture using a rotary evaporator and the precipitated solvent is filtered off with suction and dried.

5 This gives 1.48 g (76% of theory) of product.

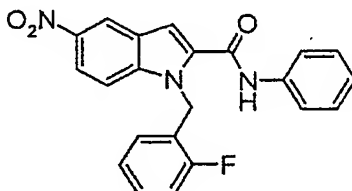
MS (DCI): $m/z = 439$ ($M+NH_4$)⁺.

¹H-NMR (300 MHz, DMSO-d₆): $\delta = 10.53$ (s, 1H), 8.74 (d, 1H), 8.17 (dd, 1H), 7.75 (d, 1H), 7.60-7.47 (m, 3H), 7.36 (m, 1H), 7.24 (t, 1H), 7.05 (t, 2H), 6.95 (d, 1H), 6.05 (s, 2H), 2.32 (s, 3H).

10

Example VII

1-(2-Fluorobenzyl)-5-nitro-N-phenyl-1H-indole-2-carboxamide



Reaction of 500 mg (1.59 mmol) of the compound from Example V and 163 mg (1.75 mmol) of aniline as described for Example VI. The reaction time is about 30 min. For work-up, the reaction mixture is poured into 100 ml of water and extracted with dichloromethane (4 × 50 ml), and the combined organic phases are dried over sodium sulphate and concentrated. Yield: 610 mg (98% of theory). For characterization, a sample of the resulting product is recrystallized from ethanol, the main quantity is directly used further.

20

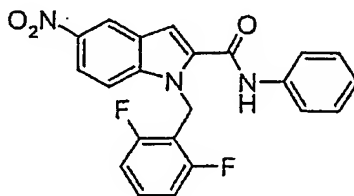
MS (DCI): $m/z = 407$ ($M+NH_4$)⁺.

¹H-NMR (400 MHz, DMSO-d₆): $\delta = 10.62$ (s, 1H), 8.81 (d, 1H), 8.16 (dd, 1H), 7.81 (d, 1H), 7.72 (d, 2H), 7.65 (s, 1H), 7.36 (t, 2H), 7.32-7.16 (m, 2H), 7.12 (t, 1H), 7.04 (dt, 1H), 6.75 (dt, 1H), 6.00 (s, 2H).

25

Example VIII

1-(2,6-Difluorobenzyl)-5-nitro-N-phenyl-1H-indole-2-carboxamide



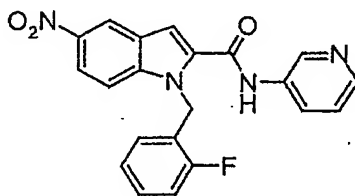
5

Preparation from the appropriate starting materials as described for Example VI.
MS (ESIpos): $m/z = 408 (M+H)^+$.

10

Example IX

1-(2-Fluorobenzyl)-5-nitro-N-(3-pyridinyl)-1H-indole-2-carboxamide



15

Preparation from the appropriate starting materials as described for Example VII. The product obtained after work-up is suspended in diethyl ether, filtered off with suction and dried.

m.p.: 234°C (decomp.)

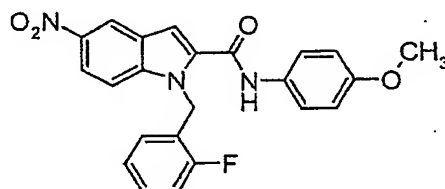
MS (ESIpos): $m/z = 391 (M+H)^+$.

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Example X

1-(2-Fluorobenzyl)-N-(4-methoxyphenyl)-5-nitro-1H-indole-2-carboxamide



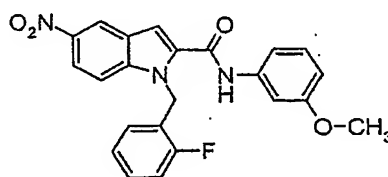
5

Preparation from the appropriate starting materials as described for Example VII. The product obtained after work-up is suspended in diethyl ether, filtered off with suction and dried.

m.p.: 233°C

10 MS (ESIpos): $m/z = 420$ (M+H)⁺.**Example XI**

1-(2-Fluorobenzyl)-N-(3-methoxyphenyl)-5-nitro-1H-indole-2-carboxamide



15

Preparation from the appropriate starting materials as described for Example VII. The product which precipitates from the reaction solution is suspended in diethyl ether, filtered off with suction and dried.

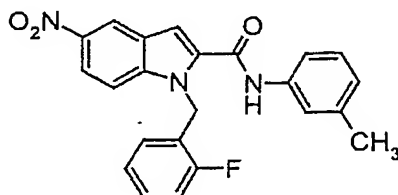
20 m.p.: 203°C

MS (ESIpos): $m/z = 420$ (M+H)⁺.

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Example XII

1-(2-Fluorobenzyl)-N-(3-methylphenyl)-5-nitro-1H-indole-2-carboxamide



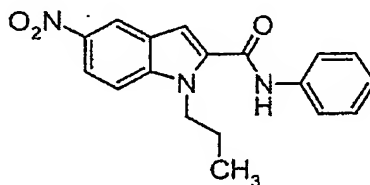
5

Preparation from the appropriate starting materials as described for Example VII. The product which precipitates from the reaction solution is suspended in diethyl ether, filtered off with suction and dried.

m.p.: 211°C

10 MS (ESIpos): $m/z = 404$ ($M+H$)⁺.**Example XIII**

5-Nitro-N-phenyl-1-propyl-1H-indole-2-carboxamide



15

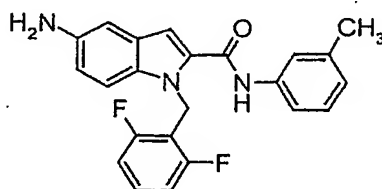
Preparation from the appropriate starting materials as described for Example VII. The product obtained after work-up is reacted further without further purification.

m.p.: 201-205°C

20 MS (ESIpos): $m/z = 324$ ($M+H$)⁺.

Example XIV

5-Amino-1-(2,6-difluorobenzyl)-N-(3-methylphenyl)-1H-indole-2-carboxamide



5

1.38 g (3.28 mmol) of the compound from Example VI are initially charged in 100 ml of ethanol. 3.70 g (16.4 mmol) of tin(II) chloride dihydrate are then added, and the mixture is stirred at the boil for 16 h. The reaction solution is poured into about 200 ml of water and made alkaline using dil. aqueous sodium hydroxide solution and extracted with ethyl acetate (5 × 50 ml). The combined org. phases are washed with 50 ml of sat. sodium chloride solution, dried over sodium sulphate and concentrated. For characterization, a sample of the resulting light-brown product (1.19 g, 85% of theory) is purified by prep. HPLC (GROM-SIL 120 OSD4 HE, 10 µm, mobile phase gradient acetonitrile-water 30:70 → 95:5), the main quantity is directly used further.

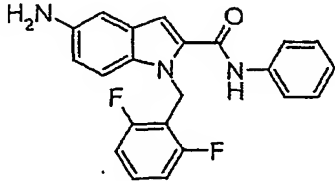
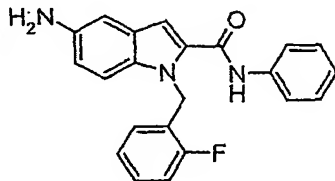
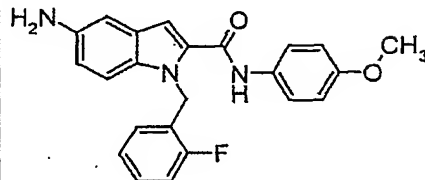
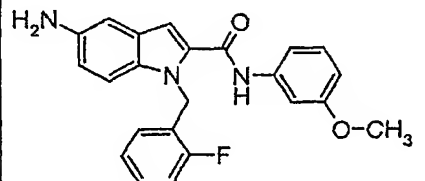
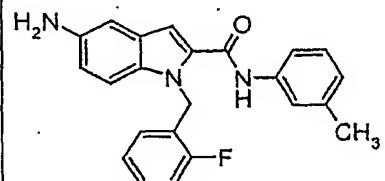
15

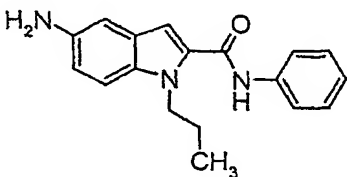
MS (ESIpos): $m/z = 392$ (M+H)⁺.

¹H-NMR (200 MHz, DMSO-d₆): δ = 10.20 (s, 1H), 7.64 (s, 1H), 7.56 (d, 1H), 7.43-7.13 (m, 3H), 7.12-6.85 (m, 4H), 6.73 (s, 1H), 6.65 (d, 1H), 5.89 (s, 2H), 4.70 (s, 2H), 2.31 (s, 3H).

20

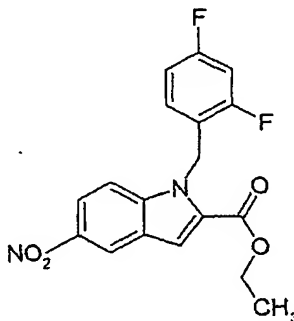
The compounds listed in the table below are prepared analogously to Example XIV.

Example	Structure	Analytical data
XV		MS (ESIpos): $m/z = 378$ (M+H) ⁺ .
XVI		m.p.: 198°C MS (ESIpos): $m/z = 360$ (M+H) ⁺ .
XVII		m.p. 222°C (decomp.) MS (ESIpos): $m/z = 390$ (M+H) ⁺ .
XVIII		m.p.: 185°C (decomp.) MS (ESIpos): $m/z = 390$ (M+H) ⁺ .
XIX		LC-MS (method MHZ2Q): $R_t = 3.19$ min MS (ESIpos): $m/z = 374$ (M+H) ⁺ .

Example	Structure	Analytical data
XX		¹ H-NMR (200 MHz, DMSO-d ₆): δ = 10.16 (s, 1H), 7.76 (d, 2H), 7.33 (m, 3H), 7.16-6.93 (m, 2H), 6.71 (m, 2H), 4.72 (br. s, 2H), 4.42 (t, 2H), 1.68 (m, 2H), 0.81 (t, 3H).

Example XXI

Ethyl 1-(2,4-difluorobenzyl)-5-nitro-1H-indole-2-carboxylate



5

Under argon, 214 mg (0.81 mmol) of 1,4,7,10,13,16-hexaoxacyclooctadecane (18-crown-6) are initially charged in 43 ml of THF, and 9.73 ml (9.73 mmol) of 1-molar potassium tert-butoxide solution in THF and 2000 mg (8.11 mmol) of ethyl 5-nitro-1H-indole-2-carboxylate are added. The mixture is stirred at RT for 15 minutes and then cooled to 0°C. A solution of 1713 mg (8.11 mmol) of 2,4-difluorobenzyl bromide in 13 ml of THF is slowly added dropwise. The ice-bath is removed and the mixture is stirred at RT for 1 hour. For work-up, the mixture is diluted with water

10

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and the THF is removed under reduced pressure using a rotary evaporator. The aqueous residue is extracted with ethyl acetate and the organic phase is washed with sat. sodium chloride solution, dried with sodium sulphate, filtered and dried under reduced pressure. The residue is purified by column chromatography (mobile phase: cyclohexane:ethyl acetate 5:1).

Yield: 888 mg (29% of theory)

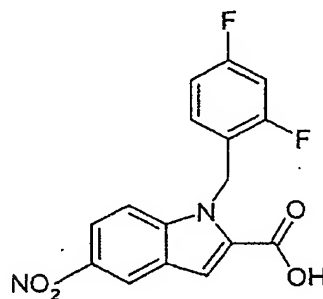
LC/MS (method 3): $R_t = 3.07$ min

MS (EI): $m/z = 361$ ($M+H$)⁺

¹H-NMR (200 MHz, DMSO- d_6): $\delta = 1.27$ (t, 3H), 4.29 (q, 2H), 5.94 (s, 2H), 6.57-6.73 (m, 1H), 6.87-7.01 (m, 1H), 7.21-7.37 (m, 1H), 7.68 (s, 1H), 7.85 (d, 1H), 8.19 (dd, 1H), 8.81 (d, 1H).

Example XXII

1-(2,4-Difluorobenzyl)-5-nitro-1H-indole-2-carboxylic acid



880 mg (2.44 mmol) of ethyl 1-(2,4-difluorobenzyl)-5-nitro-1H-indole-2-carboxylate from Example XXI are initially charged in 11 ml of THF and 11 ml of methanol. 2.44 ml (4.88 mmol) of 2-molar lithium hydroxide solution are added, and the mixture is heated at 90°C for 30 minutes. The mixture is cooled and diluted with aqueous hydrochloric acid and ethyl acetate. The organic phase is washed with sat. sodium chloride solution, dried with sodium sulphate, filtered and dried under reduced pressure.

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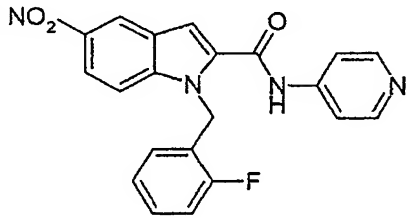
Yield: 831 mg (100% of theory)

LC/MS (method 4): $R_t = 4.26$ minMS (EI): $m/z = 331$ (M-H)⁺

5 ¹H-NMR (400 MHz, DMSO-d₆): $\delta = 5.97$ (s, 2H), 6.64 (dd, 1H), 6.90-6.98 (m, 1H),
7.24-7.32 (m, 1H), 7.59 (s, 1H), 7.78 (d, 1H), 8.15 (dd, 1H), 8.77 (dd, 1H), 13.47 (br.
s, 1H).

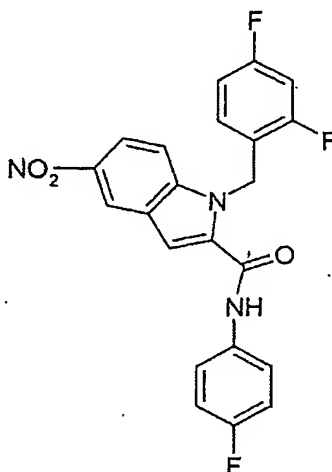
The following compound is prepared analogously to the procedure described in
Example VI:

10

Example	Structure	Analytical data
XXIII		LC/MS (method 4): $R_t = 3.08$ min MS (EI): $m/z = 391$ (M+H) ⁺

Example XXIV

1-(2,4-Difluorobenzyl)-N-(4-fluorophenyl)-5-nitro-1H-indole-2-carboxamide



5 389 mg (1.17 mmol) of 1-(2,4-difluorobenzyl)-5-nitro-1H-indole-2-carboxylic acid from Example XXII, 336 mg (1.76 mmol) of N'-(3-dimethylaminopropyl)-N-ethyl-carbodiimide \times HCl and 71.5 mg (0.59 mmol) of 4-dimethylaminopyridine are initially charged in 30 ml of a 10:1 dichloromethane:DMF mixture. 156 mg (0.13 ml, 1.40 mmol) of 4-fluoroaniline are added, and the mixture is stirred at RT for 4 hours.

10 For work-up the mixture is diluted and extracted with aqueous hydrochloric acid and ethyl acetate. The organic phase is washed with sat. sodium chloride solution, dried with sodium sulphate, filtered and dried under reduced pressure.

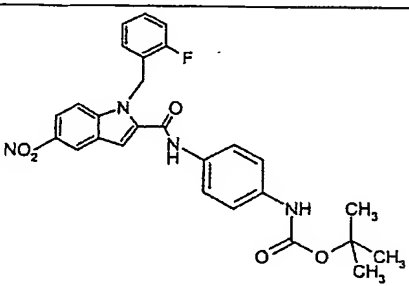
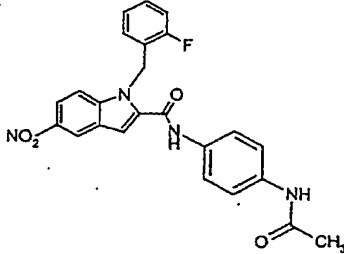
Yield: 485 mg (62% of theory)

15 LC/MS (method 1): $R_t = 5.00$ min

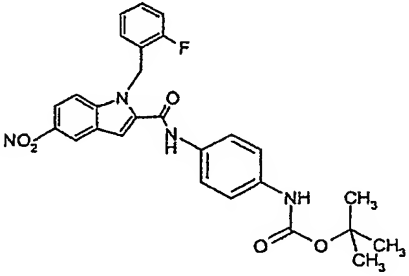
MS (EI): $m/z = 424$ (M-H)⁺

¹H-NMR (400 MHz, DMSO-d₆): $\delta = 5.94$ (s, 2H), 6.82-6.90 (m, 1H), 6.92-6.99 (m, 1H), 7.12-7.34 (m, 4H), 7.64 (s, 1H), 7.71-7.77 (m, 2H), 7.82 (d, 1H), 8.16 (dd, 1H), 8.80 (d, 1H).

The following compounds are prepared analogously to the procedure described in Example XXIV:

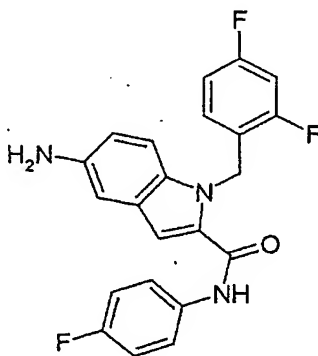
Example	Structure	Analytical data
XXV		LC/MS (method 1): $R_t = 5.17$ min MS (EI): $m/z = 503$ (M-H) ⁺
XXVI		LC/MS (method 1): $R_t = 4.40$ min MS (EI): $m/z = 447$ (M+H) ⁺

- 5 The following compound is prepared analogously to the procedure described in Example XIV:

Example	Structure	Analytical data
XXVII		HPLC (method 1): $R_t = 3.60$ min MS (EI): $m/z = 361$ ($M+H$) ⁺ ¹ H-NMR (300 MHz, DMSO- d ₆): $\delta = 4.78$ (br.s, 2H), 5.81 (s, 2H), 6.58 (t, 1H), 6.72 (dd, 1H), 6.81 (d, 1H), 6.99 (t, 1H), 7.13-7.29 (m, 4H), 7.72 (dd, 2H), 8.42 (d, 2H), 10.50 (s, 1H).

Example XXVIII

5-Amino-1-(2,4-difluorobenzyl)-N-(4-fluorophenyl)-1H-indole-2-carboxamide



5

485 mg (1.14 mmol) of 1-(2,4-difluorobenzyl)-N-(4-fluorophenyl)-5-nitro-1H-indole-2-carboxamide from Example XXIV are initially charged in ethyl acetate and ethanol. 287 mg (4.56 mmol) of ammonium formate and 49 mg of palladium on activated carbon (10%) are added. The mixture is heated to reflux, and at 50°C gas evolves. To bring the reaction to completion, the same amounts of ammonium formate and palladium as above are added. After a further 3 hours at reflux, the

10

mixture is cooled and filtered off through kieselguhr, which is washed with 500 ml of ethanol. The solvent is removed under reduced pressure and the residue is dried.

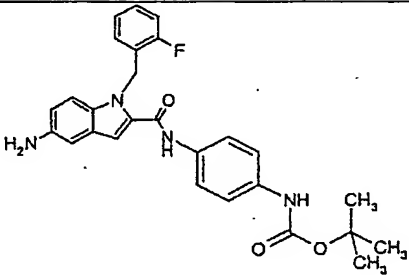
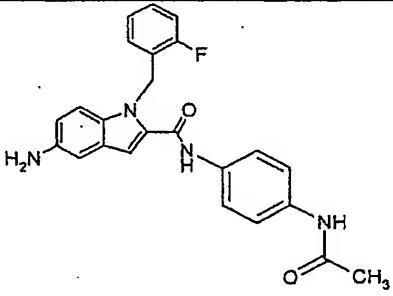
Yield: 546 mg (100% of theory)

LC/MS (method 1): $R_t = 3.40$ min

5 MS (EI): $m/z = 396$ ($M+H$)⁺

¹H-NMR (200 MHz, DMSO-d₆): $\delta = 5.76$ (s, 2H), 6.57-6.74 (m, 2H), 6.78 (s, 1H), 6.84-6.99 (m, 1H), 7.03-7.35 (m, 5H), 7.66-7.82 (m, 2H), 10.29 (s, 1H) NH₂ not detectable.

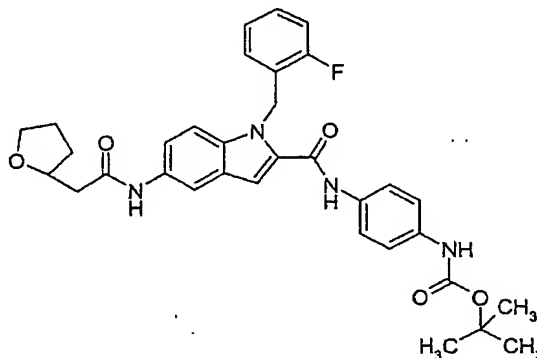
10 The following compounds are prepared analogously to the procedure described in Example XXVIII:

Example	Structure	Analytical data
XXIX		LC/MS (method 2): $R_t = 2.48$ min MS (EI): $m/z = 473$ ($M-H$) ⁺
XXX		LC/MS (method 2): $R_t = 1.52$ and 1.67 min MS (EI): $m/z = 415$ ($M-H$) ⁺

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Example XXXI

tert-Butyl 4-[(1-(2-fluorobenzyl)-5-[(tetrahydro-2-furanylacetyl)amino]-1H-indol-2-yl)carbonyl]amino]phenylcarbamate



5

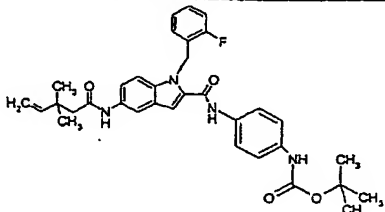
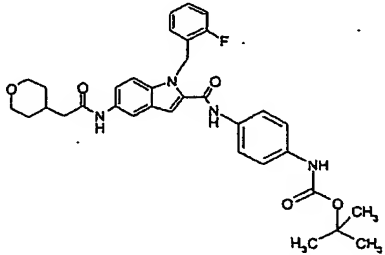
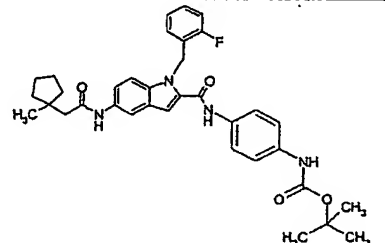
49 mg (0.38 mmol) of tetrahydro-2-furanylacetic acid, 19.3 mg (0.16 mmol) of 4-dimethylaminopyridine and 91 mg (0.47 mmol) of N'-(3-dimethylaminopropyl)-N-ethylcarbodiimide \times HCl are added to 3 ml of DMF. 150 mg (0.32 mmol) of tert-butyl 4-[(5-amino-1-(2-fluorobenzyl)-1H-indol-2-yl)carbonyl]amino]phenylcarbamate from Example XXIX are added. The mixture is stirred at RT for 5 hours. For work-up, the mixture is diluted and extracted with dichloromethane and aqueous hydrochloric acid. The organic phase is washed with sat. sodium bicarbonate solution, dried with sodium sulphate, filtered and concentrated under reduced pressure using a rotary evaporator. The residue is purified by preparative HPLC.

15 Yield: 115 mg (62% of theory)

LC/MS (method 2): $R_t = 3.57$ min

MS (EI): $m/z = 587$ ($M+H$)⁺

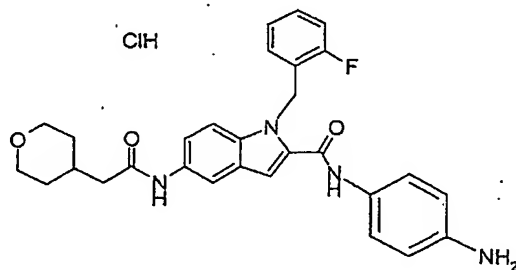
20 The following compounds are prepared analogously to the procedure described in Example XXXI:

Example	Structure	Analytical data
XXXII		LC/MS (method 1): $R_t = 5.20$ min MS (EI): $m/z = 583$ (M-H) ⁺
XXXIII		LC/MS (method 2): $R_t = 3.50$ min MS (EI): $m/z = 599$ (M-H) ⁺
XXXIV		LC/MS (method 1): $R_t = 5.42$ min MS (EI): $m/z = 597$ (M-H) ⁺

Example XXXV

N-(4-Aminophenyl)-1-(2-fluorobenzyl)-5-[(tetrahydro-2H-pyran-4-ylacetyl)amino]-
 1H-indole-2-carboxamide hydrochloride

5



121 mg (0.20 mmol) of tert-butyl-4-[(1-(2-fluorobenzyl)-5-[(tetrahydro-2H-pyran-4-ylacetyl)amino]-1H-indol-2-yl}carbonyl)amino]phenylcarbamate from Example XXXIII, 1.40 ml of dioxane and 1.40 ml of conc. hydrochloric acid are combined and stirred at RT for one hour. The mixture is evaporated to dryness using a rotary
5 evaporator.

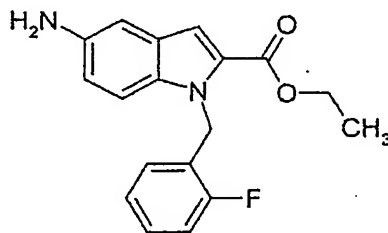
Yield: 126 mg (64% of theory)

LC/MS (method 2): $R_t = 2.22$ min

MS (EI): $m/z = 501$ ($M+H-HCl$)⁺

10 **Example XXXVI**

Ethyl 5-amino-1-(2-fluorobenzyl)-1H-indole-2-carboxylate



15 27.84 g (81.33 mmol) of ethyl 1-(2-fluorobenzyl)-5-nitro-1H-indole-2-carboxylate from Example II are initially charged in 750 ml of ethyl acetate and 750 ml of ethanol. 20.51 g (325.31 mmol) of ammonium formate and 2.78 g of palladium on activated carbon are added. The mixture is boiled at reflux and, after one hour, cooled and filtered off through kieselguhr. The filter cake is washed with ethyl
20 acetate. The solvent is removed under reduced pressure and the residue is dried.

Yield: 23.2 g (86% of theory)

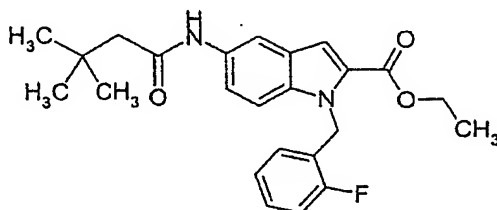
HPLC (method 6): $R_t = 4.15$ min

MS (ESIpos): $m/z = 313$ ($M+H$)⁺

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Example XXXVII

Ethyl 5-[(3,3-dimethylbutanoyl)amino]-1-(2-fluorobenzyl)-1H-indole-2-carboxylate



5

23.2 g (74.28 mmol) of ethyl 5-amino-1-(2-fluorobenzyl)-1H-indole-2-carboxylate from Example XXXVI and 15.03 g (20.71 ml, 148.56 mmol) of triethylamine are added to 300 ml of dichloromethane. The mixture is cooled to 0°C, and a solution of 11 g (11.35 ml, 81.71 mmol) of 3,3-dimethylbutyryl chloride in 300 ml of dichloromethane is added. The mixture is stirred at RT overnight and, for work-up, poured into water. The pH is adjusted to 7 and the mixture is extracted 3 times with ethyl acetate. The combined organic phases are dried over sodium sulphate, filtered and concentrated under reduced pressure.

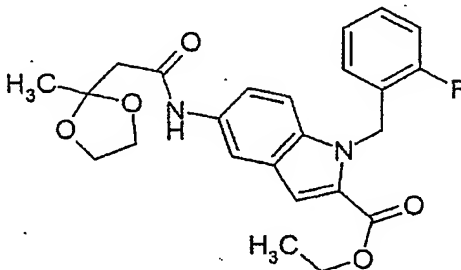
Yield: 31.7 g (100% of theory)

15 HPLC (method 6): $R_t = 5.18$ min

MS (ESIpos): $m/z = 411$ ($M+H$)⁺

Example XXXVIII

Ethyl 1-(2-fluorobenzyl)-5-[[[(2-methyl-1,3-dioxolan-2-yl)acetyl]amino]-1H-indole-2-carboxylate



5

140 mg (0.96 mmol) of (2-methyl-1,3-dioxolan-2-yl)acetic acid are added to 5 ml of DMF, and 547 mg (1.44 mmol) of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate and 186 mg (0.25 ml, 1.44 mmol) of N,N-diisopropylethylamine are added. 300 mg (0.96 mmol) of ethyl 5-amino-1-(2-fluorobenzyl)-1H-indole-2-carboxylate from Example XXXVI are added. The mixture is stirred at RT for 3 hours. For work-up the DMF is removed using a rotary evaporator. The residue is taken up in dichloromethane and extracted with aqueous hydrochloric acid. The organic phase is dried with sodium sulphate, filtered and dried under reduced pressure.

15

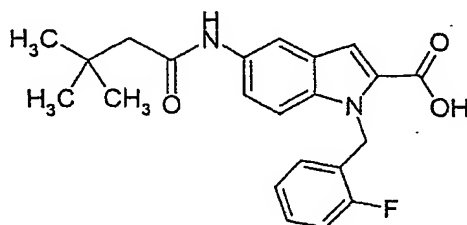
Yield: 254 mg (44% of theory)

LC/MS (method 5): $R_t = 2.98$ min

MS (EI): $m/z = 441$ ($M+H$)⁺

Example XXXIX

5-[(3,3-Dimethylbutanoyl)amino]-1-(2-fluorobenzyl)-1H-indole-2-carboxylic acid



5

Preparation analogously to Example XXII using 12.50 g (31.53 mmol) of ethyl 5-[(3,3-dimethylbutanoyl)amino]-1-(2-fluorobenzyl)-1H-indole-2-carboxylate from Example XXXVII and 31.5 ml (63.0 mmol) of 2 M lithium hydroxide solution.

Yield: 9.93 g (81% of theory)

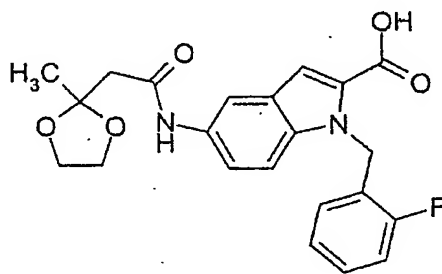
10 HPLC (method 6): $R_t = 4.57$ min

MS (ESIpos): $m/z = 383$ ($M+H$)⁺

Example XL

1-(2-Fluorobenzyl)-5-[[[(2-methyl-1,3-dioxolan-2-yl)acetyl]amino]-1H-indole-2-carboxylic acid

15



20

Preparation analogously to Example XXII using 234 mg (0.63 mmol) of ethyl 1-(2-fluorobenzyl)-5-[[[(2-methyl-1,3-dioxolan-2-yl)acetyl]amino]-1H-indole-2-carboxylate from Example XXXVIII and 0.53 ml (1.06 mmol) of lithium hydroxide solution.

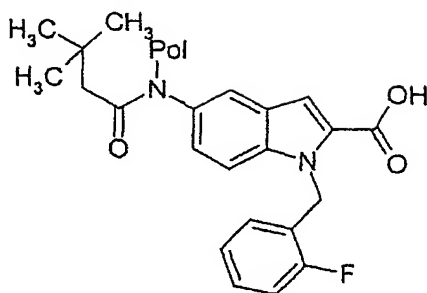
- 73 -

Yield: 198 mg (36% of theory)

LC/MS (method 1): $R_t = 4.00$ min

MS (EI): $m/z = 413$ ($M+H$)⁺

5 **Example XLI**



10 100 mg (0.08 mmol) of NovaCHO resin are initially charged in toluene/trimethyl orthoformate, and 130 mg (0.42 mmol) of ethyl 5-amino-1-(2-fluorobenzyl)-1H-indole-2-carboxylate from Example XXXVI are added. The mixture is shaken for 20 hours and then filtered off and washed with DMF. The resulting resin is initially charged in DMF, and 86 mg (0.33 mmol) of tetra-n-butylammonium borohydride are added. The mixture is shaken for 20 hours and then filtered off and washed with
15 methanol, dichloromethane/acetic acid 10/1, methanol, dichloromethane/diethyl ether 10/1, methanol and dichloromethane.

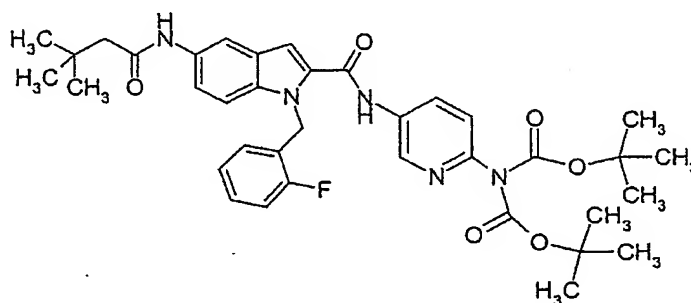
20 To 1000 mg (0.85 mmol) of the resin described above, 30 ml of dichloromethane, 1.29 g (1.77 ml, 12.75 mmol) of triethylamine and 1.14 g (1.19 ml, 8.50 mmol) of dimethylbutyryl chloride are added. The mixture is then shaken for 20 hours, filtered off with suction and washed with DMF, methanol and dichloromethane.

To 1000 mg (2.61 mmol) of the resulting resin, 15 ml of dioxane and 7.5 ml of potassium hydroxide/methanol (100 mg/ml) are added. The mixture is then shaken

over the weekend, filtered off with suction and washed with DMF, 30% strength acetic acid, methanol and dichloromethane.

Example XLII

Di-(tert-butyl) 5-(((5-[(3,3-dimethylbutanoyl)amino]-1-(2-fluorobenzyl)-1H-indol-2-yl)carbonyl)amino)-2-pyridinylimidodicarbonate



10 Di-(tert-butyl) 5-nitro-2-pyridinylimidodicarbonate:

5.0 g (35.94 mmol) of 2-amino-5-nitropyridine are dissolved in 200 ml of dichloromethane, and the mixture is cooled to 0°C. 9.29 g (12.52 ml, 71.88 mmol) of N,N-diisopropylethylamine, 19.61 g (89.86 mmol) of di-tert-butyl pyrocarbonate and 4.83 g (39.54 mmol) of 4-dimethylaminopyridine are added. The mixture is stirred at RT overnight and then diluted with ethyl acetate and washed three times with aqueous ammonium chloride solution, once with sat. sodium chloride solution, twice with aqueous sodium bicarbonate solution and once more with saturated sodium chloride solution. The organic phase is dried using sodium sulphate, filtered and concentrated under reduced pressure.

Yield: 10 g (82% of theory)

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Di-(tert-butyl) 5-amino-2-pyridinylimidodicarbonate:

7.0 g (20.63 mmol) of di-(tert-butyl) 5-nitro-2-pyridinylimidodicarbonate are dissolved in 150 ml of ethanol and 50 ml of dichloromethane. The mixture is hydrogenated at atmospheric pressure. For work-up, the mixture is filtered through a Seitz filter and washed with THF. The filtrate is dried under reduced pressure.

Yield: 5.70 g (89% of theory)

Title compound:

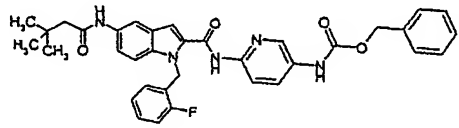
Under argon, 200 mg (0.52 mmol) of 5-[(3,3-dimethylbutanoyl)amino]-1-(2-fluorobenzyl)-1H-indole-2-carboxylic acid from Example XXXIX and 3.91 g (4 ml, 49.46 mmol) of pyridine are initially charged in 2 ml of DMF. 596 mg (1.57 mmol) of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate and 323 mg (1.05 mmol) of di-(tert-butyl) 5-amino-2-pyridinylimidodicarbonate are added. The mixture is stirred at RT overnight and the solvent is removed under reduced pressure. The residue is extracted with ethyl acetate and sat. sodium chloride solution. The organic phase is dried with sodium sulphate, filtered and dried under reduced pressure. The residue is purified by HPLC.

Yield: 111 mg (24% of theory)

LC/MS (method 2): $R_t = 4.30$ min

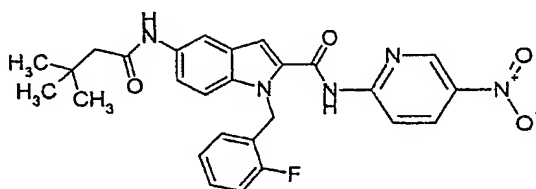
MS (EI): $m/z = 672$ (M-H)⁺

The following compound is prepared analogously to the procedure described in Example XLII (amide coupling):

Example	Structure	Analytical data
XLIII		HPLC (method 6): $R_t = 4.97$ min MS (ESIpos): $m/z = 608$ (M+H) ⁺

Example XLIV

5-[(3,3-Dimethylbutanoyl)amino]-1-(2-fluorobenzyl)-N-(5-nitro-2-pyridinyl)-1H-indole-2-carboxamide



Under argon, 400 mg (1.05 mmol) of 5-[(3,3-dimethylbutanoyl)amino]-1-(2-fluorobenzyl)-1H-indole-2-carboxylic acid from Example XXXIX are dissolved in 10 ml of DMF. The mixture is cooled to 0°C, and 202 mg (81.57 mmol) of N,N-diisopropylethylamine and 278 mg (1.26 mmol) of N,N-bis-(2-methoxyethyl)-N-(trifluoro-14-sulphonyl)amine are added. The mixture is stirred at this temperature for 15 minutes and immediately reacted further.

Half of the solution is cooled to 0°C, and 119 mg (0.86 mmol) of 5-nitro-2-pyridine-amine are added. After 15 minutes, the mixture is allowed to warm to RT and stirred for another 24 hours. For work-up, the mixture is diluted with ethyl acetate and washed 3 times with aqueous sodium bicarbonate solution. The organic phase is washed once with sat. sodium chloride solution, dried with sodium sulphate, filtered and concentrated under reduced pressure using a rotary evaporator. The residue is purified by preparative HPLC.

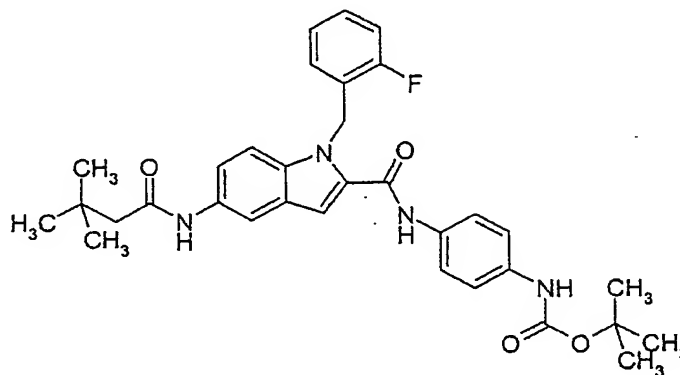
Yield: 55 mg (25% of theory)

HPLC (method 1): $R_t = 5.20$ min

MS (ESIpos): $m/z = 504$ (M+H)⁺

Example XLV

tert-Butyl 4-({[5-[(3,3-dimethylbutanoyl)amino]-1-(2-fluorobenzyl)-1H-indol-2-yl]-carbonyl}amino)phenylcarbamate



5

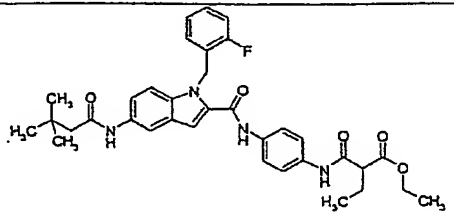
50 mg (0.13 mmol) of 5-[(3,3-dimethylbutanoyl)amino]-1-(2-fluorobenzyl)-1H-indole-2-carboxylic acid from Example XXXIX, 37.6 mg (0.20 mmol) of N³-(3-dimethylaminopropyl)-N-ethylcarbodiimide × HCl and 8 mg (0.07 mmol) of 4-dimethylaminopyridine are initially charged in DMF. 32.7 mg (0.16 mmol) of tert-butyl 4-aminophenylcarbamate are added, and the mixture is stirred at RT overnight. For work-up, the mixture is diluted and extracted with aqueous hydrochloric acid and dichloromethane. The organic phase is washed with sat. sodium chloride solution, dried with sodium sulphate, filtered and dried under reduced pressure.

15 Yield: 104 mg (82% of theory)

LC/MS (method 4): R_t = 5.20 min

MS (EI): m/z = 571 (M-H)⁺

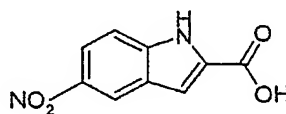
20 The following compound is prepared analogously to the procedure described in Example XLV:

Example	Structure	Analytical data
XLVI		HPLC (method 1): $R_t = 5.09$ min MS (EI): $m/z = 615$ $(M+H)^+$

Example XLVII

5-Nitro-1H-indole-2-carboxylic acid

5

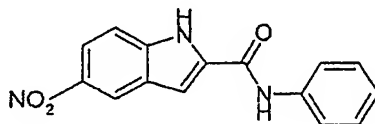


16.5 g (66.93 mmol) of ethyl 5-nitroindole-2-carboxylate are dissolved in 200 ml each of methanol and THF, and 67 ml (133.85 mmol) of lithium hydroxide solution are added. The mixture is heated at 90°C for half an hour. After cooling, the mixture is, for work-up, diluted and extracted with aqueous hydrochloric acid and ethyl acetate. The organic phase is washed with sat. sodium chloride solution, dried with sodium sulphate, filtered and dried under reduced pressure.

Yield: 15 g (100% of theory)

LC/MS (method 4): $R_t = 3.18$ minMS (EI): $m/z = 205$ $(M-H)^+$ **Example XLVIII**

5-Nitro-N-phenyl-1H-indole-2-carboxamide



20

- 79 -

5.44 g (26.39 mmol) of 5-nitro-1H-indole-2-carboxylic acid from Example XLVII, 7.59 g (39.58 mmol) of N'-(3-dimethylaminopropyl)-N-ethylcarbodiimide \times HCl and 1.61 g (13.19 mmol) of 4-dimethylaminopyridine are initially charged in 400 ml of a 10:1 dichloromethane:DMF mixture. 2.95 g (2.89 ml, 31.67 mmol) of aniline are added, and the mixture is stirred at RT overnight. For work-up, the mixture is diluted and extracted with aqueous hydrochloric acid and dichloromethane. The organic phase is washed with sat. sodium chloride solution, dried with sodium sulphate, filtered and dried under reduced pressure.

Yield: 5.83 g (75% of theory)

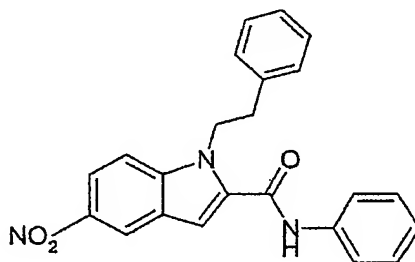
10 LC/MS (method 4): $R_t = 4.01$ min

MS (EI): $m/z = 280$ (M-H)⁺

Example XLIX

5-Nitro-N-phenyl-1-(2-phenylethyl)-1H-indole-2-carboxamide

15



Under argon, 200 mg (0.71 mmol) of 5-nitro-N-phenyl-1H-indole-2-carboxamide from Example XLVIII are initially charged in 5 ml of dimethylformamide. 85.3 mg (2.13 mmol) of sodium hydroxide (60% dispersion in paraffin) are added a little at a time, and the mixture is stirred at RT for 30 min. 657 mg (3.56 mmol) of (2-bromoethyl)benzene are then added, and the mixture is stirred at 100°C for another 5 h. To terminate the reaction, a further 3 eq. of sodium hydride and 5 eq. of bromide are added, and the mixture is stirred at 100°C for 7 hours. The reaction mixture is poured into aqueous hydrochloric acid and extracted with ethyl acetate. The organic phase is dried over sodium sulphate and the solvent is removed using a rotary

- 80 -

evaporator. The resulting crude product is purified by column chromatography (silica gel 60, mobile phase: cyclohexane/ethyl acetate 6:1).

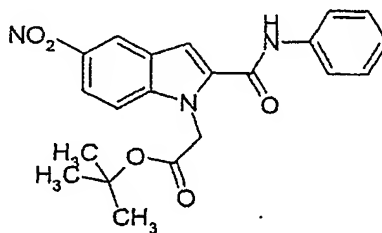
Yield: 56 mg (20% of theory)

LC/MS (method 1): $R_t = 5.05$ min

5 MS(EI): $m/z = 384$ (M-H)⁺

Example L

tert-Butyl [2-(anilinecarbonyl)-5-nitro-1H-indol-1-yl]acetate



10

Under argon, 328 mg (1.24 mmol) of 1,4,7,10,13,16-hexaoxacyclooctadecane (18-crown-6) are initially charged in 61 ml of dichloromethane, and 15 ml (14.93 mmol) of a 1-molar potassium tert-butoxide solution in THF and 3.50 g (12.44 mmol) of 5-nitro-N-phenyl-1H-indole-2-carboxamide from Example XLVIII are added. The mixture is stirred at RT for 15 minutes and then cooled to 0°C. A solution of 3.64 g (18.67 mmol) of tert-butyl bromoacetate in 100 ml of THF is slowly added dropwise. The ice-bath is removed and the mixture is stirred at RT overnight. For work-up, the mixture is diluted with water and the THF is removed under reduced pressure using a rotary evaporator. The aqueous residue is extracted with ethyl acetate and the organic phase is washed with sat. sodium chloride solution, dried with sodium sulphate, filtered and dried under reduced pressure.

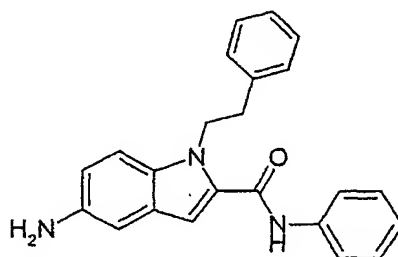
15

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Yield: 4.35 g (69% of theory)

LC/MS (method 2): L $R_t = 3.90$ min

25 MS (EI): $m/z = 418$ (M+Na)⁺

Example LI**5-Amino-N-phenyl-1-(2-phenylethyl)-1H-indole-2-carboxamide**

5

50 mg (0.13 mmol) of 5-nitro-N-phenyl-1-(2-phenylethyl)-1H-indole-2-carboxamide from Example XLIX are initially charged in 7 ml of ethyl acetate and 7 ml of ethanol. 49 mg (0.78 mmol) of ammonium formate and 14 mg of palladium on activated carbon are added. The mixture is heated to reflux, and at 50°C gas evolves. After 4 hours at reflux, the mixture is cooled and filtered through kieselguhr, which is then washed with 500 ml of ethanol. The solvent is removed under reduced pressure and the residue is dried. This gives 115 mg of a white solid which still contains inorganic salts and which is reacted further without purification.

10

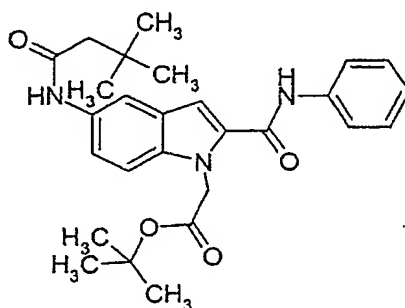
15

The following compound is prepared analogously to the procedure described in Example LI:

Example	Structure	Analytical data
LII		LC/MS (method 4): $R_t = 2.60 \text{ min}$ MS (EI): $m/z = 366$ $(M+H)^+$

Example LIII

tert-Butyl {2-(anilinecarbonyl)-5-[(3,3-dimethylbutanoyl)amino]-1H-indol-1-yl}-acetate



5

Under argon, 50 mg (0.14 mmol) of tert-butyl [5-amino-2-(anilinecarbonyl)-1H-indol-1-yl]acetate from Example LII and 15.23 mg (0.02 ml, 0.15 mmol) of triethylamine are added to 2 ml of THF. The mixture is cooled to 0°C, and a solution of 20.26 mg (0.02 ml, 0.15 mmol) of 3,3-dimethylbutyryl chloride in 0.2 ml of THF is added. The mixture is stirred at RT for 2 hours and, for work-up, added to dilute hydrochloric acid and ethyl acetate and extracted. The organic phase is washed with sat. sodium bicarbonate solution, dried with sodium sulphate, filtered and dried under reduced pressure. The resulting crude product is purified by column chromatography (silica gel 60, mobile phase: cyclohexane/ethyl acetate 2:1).

Yield: 80 mg (93% of theory)

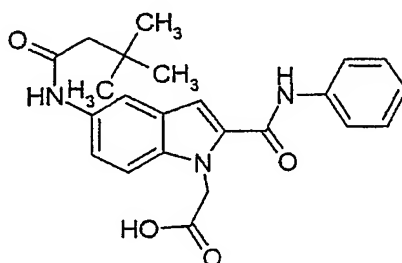
LC/MS (method 1): $R_t = 4.78$ min

MS (EI): $m/z = 464$ ($M+H$)⁺

15

Example LIV

{2-(Anilinecarbonyl)-5-[(3,3-dimethylbutanoyl)amino]-1H-indol-1-yl} acetic acid



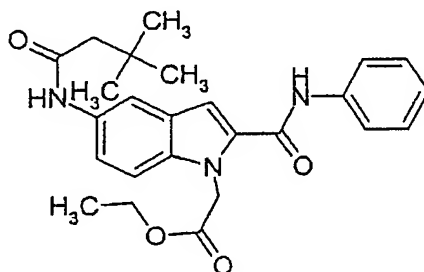
5

70 mg (0.15 mmol) of tert-butyl {2-(anilinecarbonyl)-5-[(3,3-dimethylbutanoyl)-amino]-1H-indol-1-yl} acetate from Example LIII, 0.50 ml of trifluoroacetic acid and 1 ml of dichloromethane are stirred together at RT for one hour. The solvent is removed under reduced pressure and the residue is dried in vacuo.

10 Yield: 86.7 mg (100% of theory)
LC/MS (method 1): $R_t = 4.43$ min
MS (EI): $m/z = 408$ ($M+H$)⁺

Example LV

15 Ethyl {2-(anilinecarbonyl)-5-[(3,3-dimethylbutanoyl)amino]-1H-indol-1-yl} acetate



20 1.50 g (3.68 mmol) of {2-(anilinecarbonyl)-5-[(3,3-dimethylbutanoyl)amino]-1H-indol-1-yl} acetic acid from Example LIV, 225 mg (1.84 mmol) of 4-dimethylamino-

- 84 -

pyridine and 203.5 mg (4.42 mmol) of ethanol are initially charged in dichloromethane. The mixture is cooled to 0°C, and 776 mg (4.05 mmol) of N'-(3-dimethylaminopropyl)-N-ethylcarbodiimide × HCl are added. The mixture is stirred at RT for 4 hours. For work-up, the mixture is diluted and extracted with water and dichloromethane. The organic phase is dried with sodium sulphate, filtered and dried under reduced pressure. The resulting crude product is purified by column chromatography (silica gel 60, mobile phase: cyclohexane/ethyl acetate 2:1-1:1).

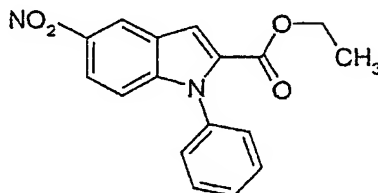
Yield: 227 mg (14% of theory)

LC/MS (method 4): $R_t = 4.60$ min

MS (EI): $m/z = 436$ ($M+H$)⁺

Example LVI

Ethyl 5-nitro-1-phenyl-1H-indole-2-carboxylate



5.5 g (22.31 mmol) of ethyl 5-nitro-1H-indole-2-carboxylate, 6.16 g (44.62 mmol) of anhydrous potassium carbonate, 77.53 g (52 ml, 493.8 mmol) of bromobenzene and 1.6 g (11.15 mmol) of copper bromide are stirred under reflux (about 156°C) for 5 days. The reaction mixture is then filtered, and the residue on the frit is washed with toluene. The collected filtrates are concentrated, dried under high vacuum and purified by flash chromatography on silica gel.

Yield: 5.71 g (82% of theory)

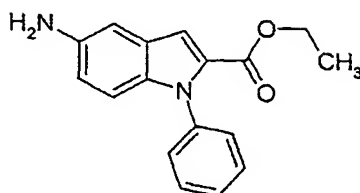
LC/MS (method 1): $R_t = 5.14$ min

MS (EI): $m/z = 309$ ($M-H$)⁺

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Example LVII

Ethyl 5-amino-1-phenyl-1H-indole-2-carboxylate



5

300 mg (0.97 mmol) of ethyl 5-nitro-1-phenyl-1H-indole-2-carboxylate from Example LVI are initially charged in 40 ml of ethyl acetate and 40 ml of ethanol. 365 mg (5.80 mmol) of ammonium formate and 102 mg of palladium on activated carbon (10%) are added. The mixture is heated to reflux, and at 50°C gas evolves. After 4 hours at reflux, the mixture is cooled and filtered off through kieselguhr, which is washed with 500 ml of ethanol. The solvent is removed under reduced pressure and the residue is dried.

10

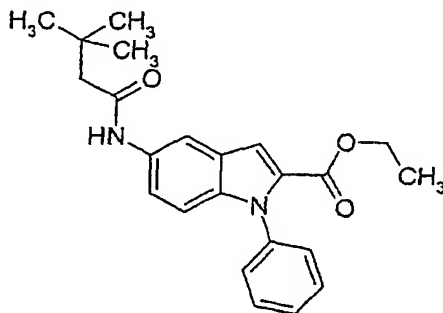
Yield: 355 mg (93% of theory)

LC/MS (method 5): $R_t = 2.17$ min

15

MS (EI): $m/z = 281$ ($M+H$)⁺**Example LVIII**

Ethyl 5-[(3,3-dimethylbutanoyl)amino]-1-phenyl-1H-indole-2-carboxylate



20

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Under argon, 355 mg (1.27 mmol) of ethyl 5-amino-1-phenyl-1H-indole-2-carboxylate from Example LVII and 141 mg (0.19 ml, 1.39 mmol) of triethylamine are added to 4 ml of THF. The mixture is cooled to 0°C, and a solution of 170 mg (0.18 ml, 1.27 mmol) of 3,3-dimethylbutyryl chloride in 2 ml of THF is added. The mixture is stirred at RT for 2 hours. To bring the reaction to completion, a further 1 eq. of triethylamine and 1 eq. of acid chloride are added and the mixture is stirred at RT for 2 hours. For work-up, the mixture is added to dilute hydrochloric acid and ethyl acetate and extracted. The organic phase is washed with sat. sodium bicarbonate solution, dried with sodium sulphate, filtered and dried under reduced pressure. The resulting crude product is purified by column chromatography (silica gel 60, mobile phase: cyclohexane/ethyl acetate 3:1-1:1).

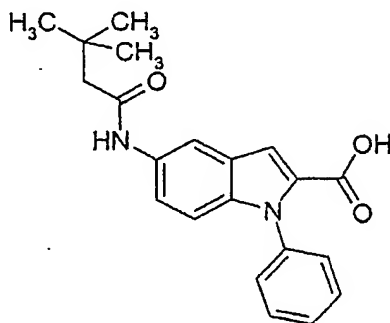
Yield: 118 mg (25% of theory)

LC/MS (method 5): $R_t = 3.54$ min

MS (EI): $m/z = 379$ ($M+H$)⁺

Example LIX

5-[(3,3-Dimethylbutanoyl)amino]-1-phenyl-1H-indole-2-carboxylic acid



119 mg (0.31 mmol) of ethyl 5-[(3,3-dimethylbutanoyl)amino]-1-phenyl-1H-indole-2-carboxylate from Example LVIII are dissolved in each case in 2 ml of methanol and THF, and 0.31 ml (0.63 mmol) of a 2 M lithium hydroxide solution is added.

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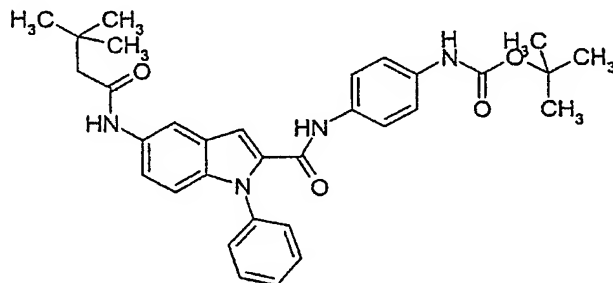
The mixture is heated at 90°C for one hour. After cooling, the mixture is, for work-up, diluted and extracted with aqueous hydrochloric acid and ethyl acetate. The organic phase is dried with sodium sulphate, filtered and dried under reduced pressure.

5 Yield: 151 mg (100% of theory)

¹H-NMR (200 MHz, DMSO-d₆): δ = 1.03 (s, 9H), 2.18 (s, 2H), 6.96 (d, 1H), 7.31-7.40 (m, 3H), 7.46-7.59 (m, 4H), 8.15 (s, 1H), 9.77 (s, 1H), 12.73 (br. s, 1H).

Example LX

10 tert-Butyl 4-[(5-[(3,3-dimethylbutanoyl)amino]-1-phenyl-1H-indol-2-yl)carbonyl)-amino]phenylcarbamate



15 75 mg (0.21 mmol) of 5-[(3,3-dimethylbutanoyl)amino]-1-phenyl-1H-indole-2-carboxylic acid from Example LIX, 61.55 mg (0.32 mmol) of N'-[(3-dimethylaminopropyl)-N-ethylcarbodiimide] × HCl and 13.1 mg (0.11 mmol) of 4-dimethylaminopyridine are initially charged in 4 ml of dichloromethane. 44.6 mg (0.21 mmol) of tert-butyl 4-aminophenylcarbamate are added, and the mixture is

20 stirred at RT for 3 hours. For work-up, the mixture is diluted and extracted with aqueous hydrochloric acid and dichloromethane. The organic phase is dried with sodium sulphate, filtered and dried under reduced pressure.

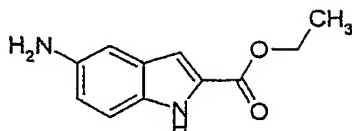
Yield: 87 mg (60% of theory)

LC/MS (method 4): R_t = 5.02 min

25 MS (EI): m/z = 539 (M-H)⁺

Example LXI

Ethyl 5-amino-1H-indole-2-carboxylate



5

Under argon, 15 g (60.84 mmol) of ethyl 5-nitro-1H-indole-2-carboxylate are initially charged in 750 ml of ethyl acetate and 750 ml of ethanol. 15.82 g (15.82 mmol) of ammonium formate and 1.50 g of palladium on activated carbon (10%) are added. The mixture is stirred at 90°C for 30 minutes and then cooled and filtered off through Celite, which is washed with ethyl acetate. The solvent is removed under reduced pressure and the residue is dissolved in chloroform and washed twice with water. The organic phase is dried with sodium sulphate, filtered and concentrated under reduced pressure using a rotary evaporator.

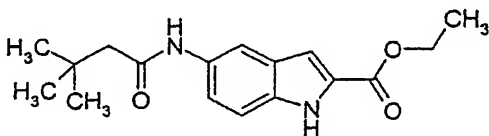
15 Yield: 12.81 g (100% of theory)

LC/MS (method 4): $R_t = 0.37$ minMS (EI): $m/z = 205$ ($M+H$)⁺¹H-NMR (200 MHz, DMSO-d₆): $\delta = 1.31$ (t, 3H), 4.29 (q, 2H), 4.67 (s, 2H), 6.62-6.76 (m, 2H), 6.79-6.88 (m, 1H), 7.11-7.22 (m, 1H), 11.41 (br. s, 1H).

20

Example LXII

Ethyl 5-[(3,3-dimethylbutanoyl)amino]-1H-indole-2-carboxylate



25

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3.76 g (18.4 mmol) of ethyl 5-amino-1H-indole-2-carboxylate from Example LXI and 2.05 g (2.82 ml, 20.3 mmol) of triethylamine are added to 40 ml of THF. The mixture is cooled to 0°C, and a solution of 2.48 g (2.56 ml, 18.4 mmol) of 3,3-dimethylbutyryl chloride in 20 ml of THF are added. The mixture is stirred at RT for 2 h and, for work-up, poured into water. The pH is adjusted to 7 and the mixture is extracted 3 times with ethyl acetate. The combined organic phases are dried with sodium sulphate, filtered and dried under reduced pressure.

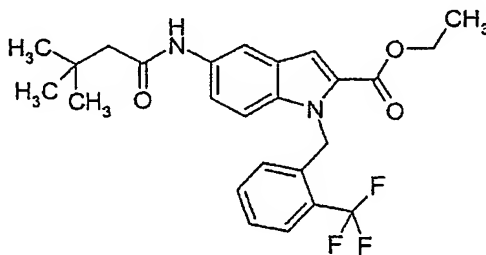
Yield: 5.49 g (98% of theory)

HPLC (method 4): $R_t = 4.20$ min

MS (ESIpos): $m/z = 303$ (M+H)⁺

Example LXIII

Ethyl 5-[(3,3-dimethylbutanoyl)amino]-1-[2-(trifluoromethyl)benzyl]-1H-indole-2-carboxylate



Under argon, 35 mg (0.13 mmol) of 1,4,7,10,13,16-hexaoxacyclooctadecane (18-crown-6) are initially charged in 7 ml of THF, and 1.98 ml (1.98 mmol) of a 1-molar potassium tert-butoxide solution in THF and 400 mg (1.32 mmol) of ethyl 5-[(3,3-dimethylbutanoyl)amino]-1H-indole-2-carboxylate from Example LXII are added. The mixture is stirred at RT for 15 minutes and cooled to 0°C. A solution of 474 mg (1.98 mmol) of 2-trifluoromethylbenzyl bromide in 12 ml of THF is slowly added dropwise. The ice-bath is removed and the mixture stirred at RT for 1 hour. For work-up, the mixture is diluted with water and the THF is removed under reduced pressure using a rotary evaporator. The aqueous residue is extracted with ethyl acetate and the organic phase is washed with sat. sodium chloride solution, dried

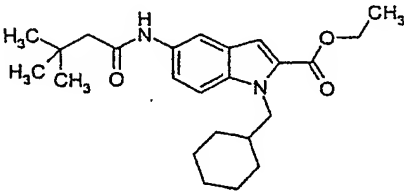
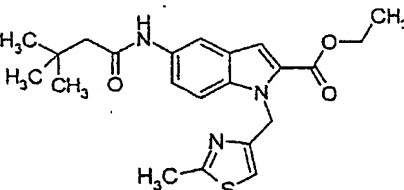
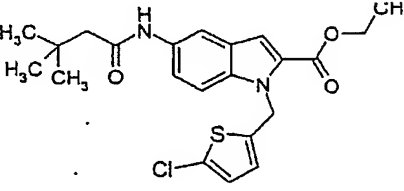
with sodium sulphate, filtered and dried under reduced pressure. The residue is purified by column chromatography (mobile phase: cyclohexane:ethyl acetate 5:1).

Yield: 238 mg (39% of theory)

HPLC (method 5): $R_t = 3.60$ min

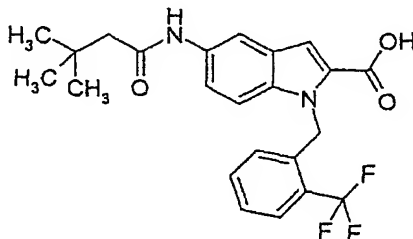
5 MS (ESIpos): $m/z = 461$ ($M+H$)⁺

The following compounds are prepared analogously to the procedure described in Example LXIII:

Example	Structure	Analytical data
LXIV		LC/MS (method 1): $R_t = 5.50$ min MS (EI): $m/z = 399$ ($M+H$) ⁺
LXV		LC/MS (method 2): $R_t = 3.55$ min MS (EI): $m/z = 414$ ($M+H$) ⁺
LXVI		LC/MS (method 2): $R_t = 4.18$ min MS (EI): $m/z = 433$ ($M+H$) ⁺

Example LXVII

5-[(3,3-Dimethylbutanoyl)amino]-1-[2-(trifluoromethyl)benzyl]-1H-indole-2-carboxylic acid



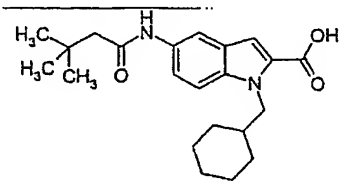
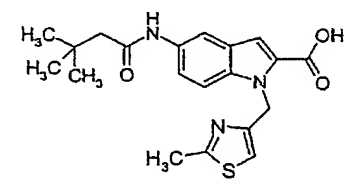
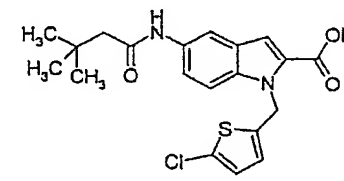
5

105 mg (0.26 mmol) of ethyl 5-[(3,3-dimethylbutanoyl)amino]-1-[2-(trifluoromethyl)benzyl]-1H-indole-2-carboxylate from Example LXIII are dissolved in 1 ml each of methanol and THF, and 0.26 ml (0.52 mmol) of 2M lithium hydroxide solution is added. The mixture is heated at 90°C for one hour. After cooling, the mixture is, for work-up, diluted and extracted with aqueous hydrochloric acid and ethyl acetate. The organic phase is dried with sodium sulphate, filtered and dried under reduced pressure.

Yield: 89 mg (89% of theory)
HPLC (method 4): $R_t = 4.76$ min
MS (ESIpos): $m/z = 433$ ($M+H$)⁺

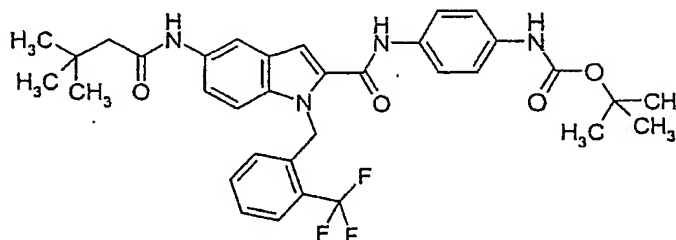
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The following compounds are prepared analogously to the procedure described in Example LXVII

Example	Structure	Analytical data
LXVIII		LC/MS (method 1): $R_t = 5.80$ min MS (EI): $m/z = 371$ ($M+H$) ⁺
LXIX		LC/MS (method 4): $R_t = 3.95$ min MS (EI): $m/z = 386$ ($M+H$) ⁺
LXX		¹ H-NMR (200 MHz, DMSO-d ₆): $\delta = 1.05$ (s, 9H), 2.19 (s, 2H), 5.89 (s, 2H), 5.95 (s, 2H), 6.98 (d, 2H), 7.03 (d, 1H), 7.22 (s, 1H), 7.39 (dd, 1H), 7.68 (d, 1H), 8.06 (dd, 1H), 9.78 (s, 1H).

Example LXXI

tert-Butyl 4-[(5-[(3,3-dimethylbutanoyl)amino]-1-[2-(trifluoromethyl)benzyl]-1H-indol-2-yl)carbonyl]aminophenylcarbamate



5

125 mg (0.29 mmol) of 5-[(3,3-dimethylbutanoyl)amino]-1-[2-(trifluoromethyl)-benzyl]-1H-indole-2-carboxylic acid from Example LXVII, 83 mg (0.43 mmol) of N'-(3-dimethylaminopropyl)-N-ethylcarbodiimide \times HCl and 17.7 mg (0.14 mmol) of 4-dimethylaminopyridine are initially charged in 6 ml of dichloromethane. 60 mg (0.29 mmol) of tert-butyl 4-aminophenylcarbamate are added, and the mixture is stirred at RT for 4 hours. For work-up, the mixture is diluted and extracted with aqueous hydrochloric acid and ethyl acetate. The organic phase is washed with sat. sodium chloride solution, dried with sodium sulphate, filtered and dried under reduced pressure.

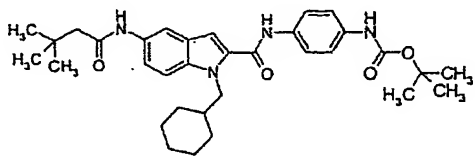
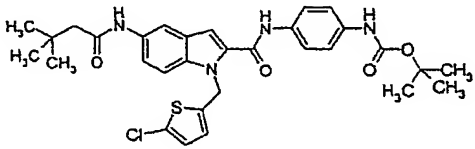
15

Yield: 158 mg (87% of theory)

LC/MS (method 1): $R_t = 5.40$ min

MS (EI): $m/z = 645$ ($M+Na$)⁺

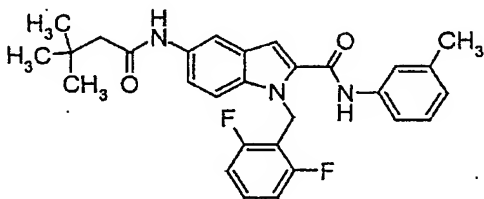
20 The following compounds are prepared analogously to the procedure described in Example LXXI:

Example	Structure	Analytical data
LXXII		LC/MS (method 1): $R_t = 5.50$ min MS (EI): $m/z = 561$ (M+H) ⁺
LXXIII		LC/MS (method 1): $R_t = 5.40$ min MS (EI): $m/z = 595$ (M+H) ⁺

Preparation Examples

Example 1

1-(2,6-Difluorobenzyl)-5-[(3,3-dimethylbutanoyl)amino]-N-(3-methylphenyl)-1H-indole-2-carboxamide



59 mg (0.150 mmol) of the compound from Example XIV and 0.04 ml (0.30 mmol) of triethylamine are initially charged in 5 ml of dichloromethane. At 0°C, a solution of 26 mg of 3,3-dimethylbutyryl chloride (0.195 mmol) in 1 ml of dichloromethane is added dropwise, and the mixture is stirred at RT for 30 min. The reaction solution is concentrated and the residue is purified chromatographically on silica gel 60 (mobile phase gradient cyclohexane → cyclohexane:ethyl acetate 2.5:1). The resulting product is taken up in a little ethyl acetate, precipitated by addition of n-pentane, filtered off with suction and dried. This gives 35 mg (45% of theory) of a light-beige solid.

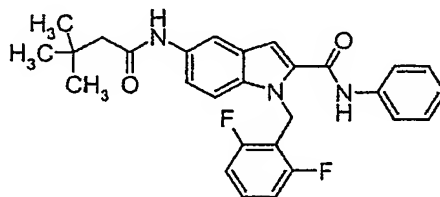
MS (ESIpos): $m/z = 490$ ($M+H$)⁺

¹H-NMR (300 MHz, DMSO-d₆): $\delta = 10.23$ (s, 1H), 9.68 (s, 1H), 8.01 (d, 1H), 7.62 (s, 1H), 7.55 (d, 1H), 7.45-7.29 (m, 3H), 7.23 (t, 1H), 7.19 (s, 1H), 7.03 (t, 2H), 6.92 (d, 1H), 5.96 (s, 2H), 2.32 (s, 3H), 2.18 (s, 2H), 1.03 (s, 9H).

The examples below are prepared in a manner analogous to Example 1 using the appropriate starting materials:

Example 2

1-(2,6-Difluorobenzyl)-5-[(3,3-dimethylbutanoyl)amino]-N-phenyl-1H-indole-2-carboxamide



5

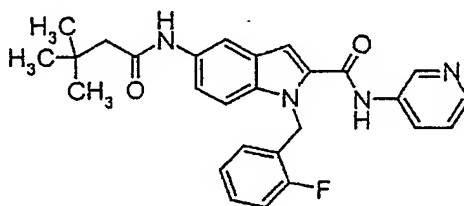
MS (ESIpos): $m/z = 476 (M+H)^+$

$^1\text{H-NMR}$ (300 MHz, DMSO-d_6): $\delta = 10.35$ (s, 1H), 9.68 (s, 1H), 8.01 (d, 1H), 7.77 (d, 2H), 7.35 (m, 5H), 7.20 (s, 1H), 7.05 (m, 3H), 2.18 (s, 2H), 1.03 (s, 9H).

10

Example 3

5-[(3,3-Dimethylbutanoyl)amino]-1-(2-fluorobenzyl)-N-(3-pyridinyl)-1H-indole-2-carboxamide



15

MS (ESIpos): $m/z = 459 (M+H)^+$

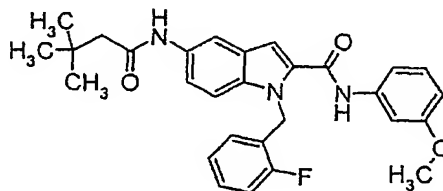
$^1\text{H-NMR}$ (200 MHz, DMSO-d_6): $\delta = 10.57$ (s, 1H), 9.77 (s, 1H), 8.88 (d, 1H), 8.30 (d, 1H), 8.20-8.09 (m, 2H), 7.53-7.12 (m, 6H), 7.01 (dt, 1H), 6.60 (t, 1H), 5.90 (s, 2H), 2.19 (s, 2H), 1.04 (s, 9H).

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Example 4

5-[(3,3-Dimethylbutanoyl)amino]-1-(2-fluorobenzyl)-N-(3-methoxyphenyl)-1H-indole-2-carboxamide

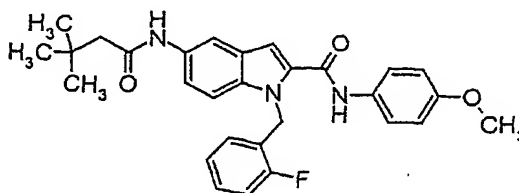


MS (ESIpos): $m/z = 488$ ($M+H$)⁺

¹H-NMR (300 MHz, DMSO-d₆): $\delta = 10.30$ (s, 1H), 9.71 (s, 1H), 8.08 (d, 1H), 7.48-7.14 (m, 8H), 7.00 (dt, 1H), 6.67 (ddd, 1H), 6.61 (dt, 1H), 5.89 (s, 2H), 3.74 (s, 3H), 2.19 (s, 2H), 1.04 (s, 9H).

Example 5

5-[(3,3-Dimethylbutanoyl)amino]-1-(2-fluorobenzyl)-N-(4-methoxyphenyl)-1H-indole-2-carboxamide

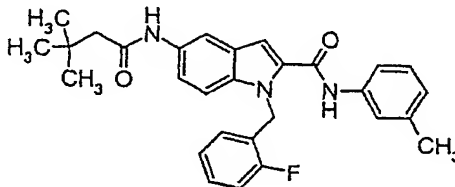


MS (ESIpos): $m/z = 488$ ($M+H$)⁺

¹H-NMR (300 MHz, DMSO-d₆): $\delta = 10.21$ (s, 1H), 9.70 (s, 1H), 8.07 (d, 1H), 7.61 (m, 2H), 7.43 (d, 1H), 7.33 (m, 2H), 7.21 (m, 2H), 7.00 (dt, 1H), 6.90 (m, 2H), 6.60 (dt, 1H), 5.89 (s, 2H), 3.74 (s, 3H), 2.19 (s, 2H), 1.04 (s, 9H).

Example 6

5-[(3,3-Dimethylbutanoyl)amino]-1-(2-fluorobenzyl)-N-(3-methylphenyl)-1H-indole-2-carboxamide

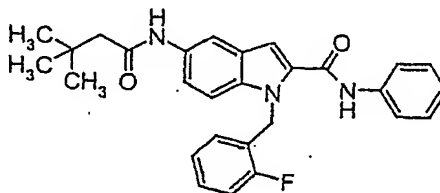


MS (ESIpos): $m/z = 472 (M+H)^+$

$^1\text{H-NMR}$ (300 MHz, DMSO-d_6): $\delta = 10.24$ (s, 1H), 9.70 (s, 1H), 8.08 (d, 1H), 7.58 (m, 1H), 7.50 (d, 1H), 7.44 (d, 1H), 7.38-7.14 (m, 5H), 7.00 (dt, 1H), 6.91 (d, 1H), 6.60 (dt, 1H), 5.89 (s, 2H), 2.30 (s, 3H), 2.19 (s, 2H), 1.04 (s, 9H).

Example 7

5-[(3,3-Dimethylbutanoyl)amino]-1-(2-fluorobenzyl)-N-phenyl-1H-indole-2-carboxamide



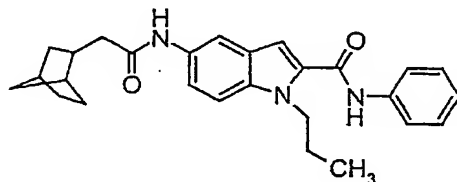
MS (ESIpos): $m/z = 458 (M+H)^+$

$^1\text{H-NMR}$ (300 MHz, DMSO-d_6): $\delta = 10.31$ (s, 1H), 9.71 (s, 1H), 8.08 (s, 1H), 7.72 (d, 2H), 7.47-7.14 (m, 7H), 7.09 (t, 1H), 7.00 (t, 1H), 6.61 (t, 1H), 5.90 (s, 2H), 2.19 (s, 2H), 1.04 (s, 9H).

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Example 8

5-[(Bicyclo[2.2.1]hept-2-ylacetyl)amino]-N-phenyl-1-propyl-1H-indole-2-carboxamide

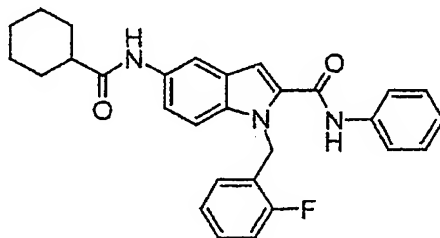


MS (ESIpos): $m/z = 430$ ($M+H$)⁺

¹H-NMR (300 MHz, DMSO-d₆): $\delta = 10.25$ (s, 1H), 9.75 (s, 1H), 8.03 (s, 1H), 7.77 (d, 2H), 7.52 (d, 1H), 7.42-7.30 (m, 3H), 7.23 (s, 1H), 7.10 (dd, 1H), 4.50 (t, 2H), 2.40-2.09 (m, 5H), 1.84-1.06 (m, 11H), 0.81 (t, 3H), 0.73 (m, 1H).

Example 9

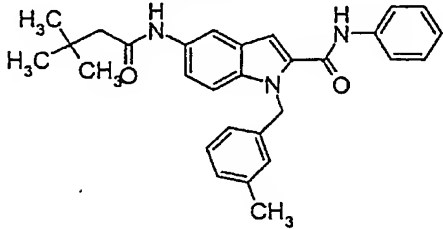
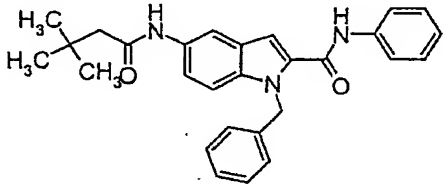
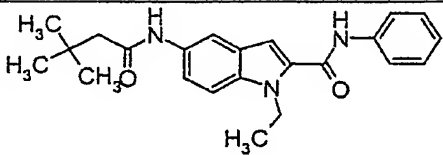
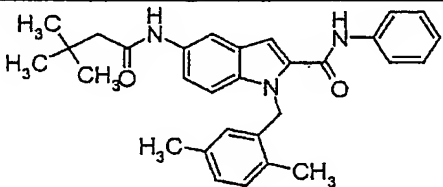
5-[(Cyclohexylcarbonyl)amino]-1-(2-fluorobenzyl)-N-phenyl-1H-indole-2-carboxamide

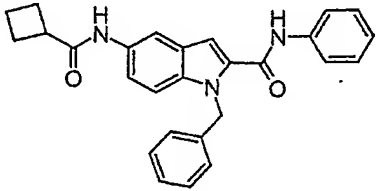
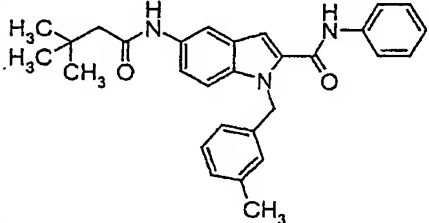
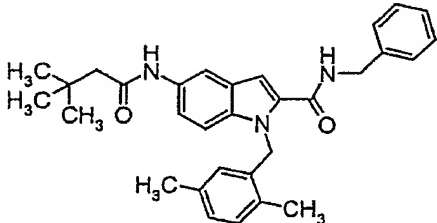
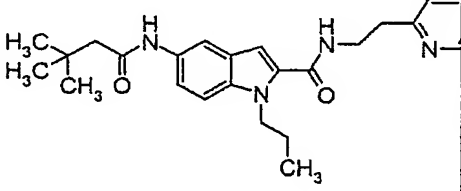
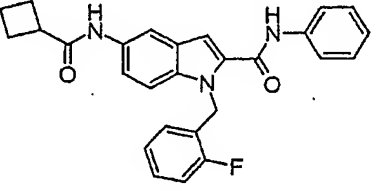


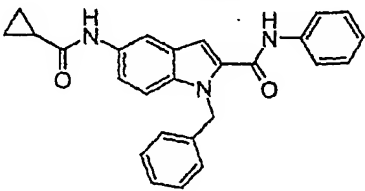
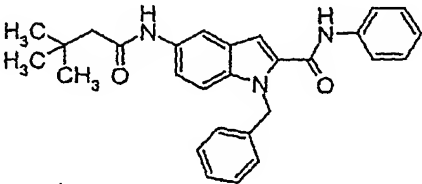
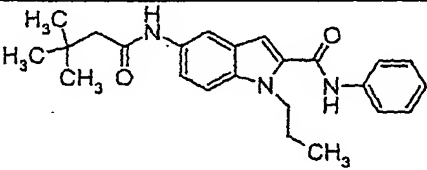
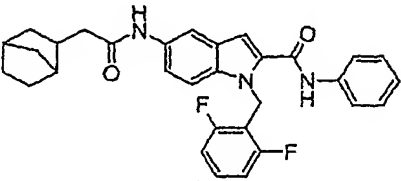
MS (ESIpos): $m/z = 470$ ($M+H$)⁺

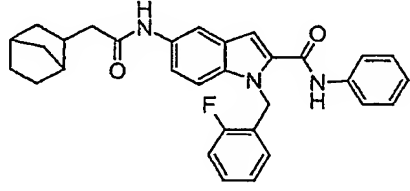
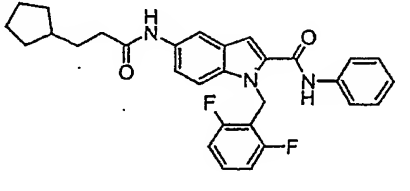
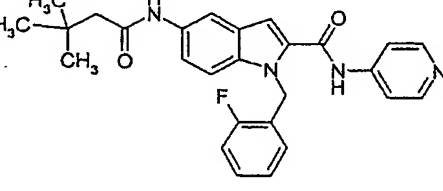
¹H-NMR (300 MHz, DMSO-d₆): $\delta = 10.32$ (s, 1H), 9.71 (s, 1H), 8.11 (d, 1H), 7.72 (d, 2H), 7.47-7.13 (m, 7H), 7.08 (t, 1H), 6.98 (dt, 1H), 6.59 (dt, 1H), 5.90 (s, 2H), 2.33 (m, 1H), 1.88-1.60 (m, 5H), 1.52-1.15 (m, 5H).

The examples listed in the table below can be prepared analogously to the procedure described above using the appropriate starting materials.

Example	Structure	Analytical data
10		LC-MS (method MHZ2Q): $R_t = 4.93$ min $m/z = 454$ (M+H) ⁺
11		
12		LC-MS (method MHZ2Q): $R_t = 4.51$ min $m/z = 378$ (M+H) ⁺
13		

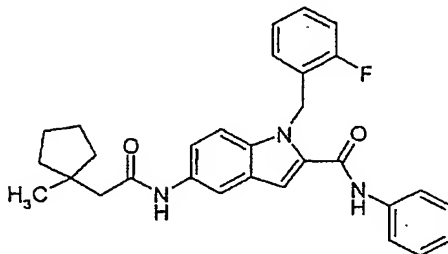
Example	Structure	Analytical data
14		
15		
16		
17		LC-MS (method MHZ2Q): $R_t = 2.96 \text{ min}$ $m/z = 421 (M+H)^+$
18		

Example	Structure	Analytical data
19		LC-MS (method MHZ2Q): $R_t = 4.42 \text{ min}$ $m/z = 410 (M+H)^+$
20		LC-MS (method MHZ2Q): $R_t = 4.79 \text{ min}$ $m/z = 440 (M+H)^+$
21		MS (ESIpos): $m/z = 392 (M+H)^+$. $^1\text{H-NMR}$ (200 MHz, DMSO- d_6): $\delta = 10.30$ (s, 1H), 9.71 (s, 1H), 8.07 (s, 1H), 7.78 (d, 2H), 7.51 (d, 1H), 7.33 (m, 3H), 7.21 (s, 1H), 7.09 (dd, 1H), 4.50 (t, 2H), 2.19 (s, 2H), 1.70 (sextet, 2H), 1.04 (s, 9H), 0.80 (t, 3H).
22		MS (ESIpos): $m/z = 514 (M+H)^+$. $^1\text{H-NMR}$ (200 MHz, DMSO- d_6): $\delta = 10.39$ (s, 1H), 9.81 (s, 1H), 8.03 (d, 1H), 7.75 (d, 2H), 7.51-6.95 (m, 6H), 6.58 (t, 1H), 5.92 (s, 2H), 2.45-2.05 (m, 5H), 1.80-1.00 (m, 8H), 0.71 (m, 1H).

Example	Structure	Analytical data
23		MS (ESIpos): $m/z = 496$ $(M+H)^+$. $^1\text{H-NMR}$ (200 MHz, CDCl_3): $\delta = 8.08$ (s, 1H), 7.92 (s, 1H), 7.61 (d, 2H), 7.48-6.85 (m, 7H), 6.72 (t, 1H), 5.89 (s, 2H), 2.49-2.11 (m, 5H), 1.68-1.05 (m, 8H), 0.73 (m, 1H).
24		MS (ESIpos): $m/z = 502$ $(M+H)^+$. $^1\text{H-NMR}$ (200 MHz, DMSO-d_6): $\delta = 10.39$ (s, 1H), 9.80 (s, 1H), 8.02 (s, 1H), 7.77 (d, 2H), 7.49-7.22 (m, 5H), 7.21-6.91 (m, 4H), 5.94 (s, 2H), 2.29 (t, 2H), 1.88-1.35 (m, 8H), 1.30-0.97 (m, 2H).
25		HPLC (SYA-HPPSK2): R_t = 4.43 min. MS (ESIpos): $m/z =$ 459.1 $(M+H)^+$. $^1\text{H-NMR}$ (200 MHz, DMSO-d_6): $\delta = 1.04$ (s, 9H), 2.19 (s, 2H), 5.89 (s, 2H), 6.59 (t, 1H), 7.01 (t, 1H), 7.15-7.54 (m, 5H), 7.73 (d, 2H), 8.12 (s, 1H), 8.45 (d, 2H), 9.78 (s, 1H), 10.69 (s, 1H).

Example 26

1-(2-Fluorobenzyl)-5-[[[(1-methylcyclopentyl)acetyl]amino}-N-phenyl-1H-indole-2-carboxamide



5

62 mg (0.20 mmol) of the compound from Example XXVI, 58 mg (0.30 mmol) of N¹-(3-dimethylaminopropyl)-N-ethylcarbodiimide × HCl and 12 mg (0.1 mmol) of 4-dimethylaminopyridine are initially charged in DMF. 34 mg (0.24 mmol) of (1-methylcyclopentyl)acetic acid (synthesized according to K. Bott, *Chem. Ber.* 1967, 100, 978-983) are added, and the mixture is stirred at RT for 5 h. For work-up, the mixture is diluted and extracted with aqueous hydrochloric acid and dichloromethane. The organic phase is washed with sat. sodium chloride solution, dried with sodium sulphate, filtered and dried under reduced pressure. Purification is carried out by flash chromatography on silica gel.

15

Yield: 56 mg (57% of theory)

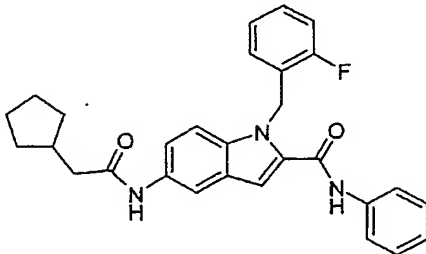
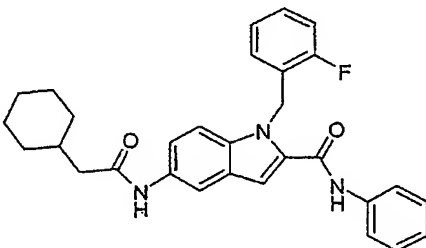
LC/MS (SMKL-ZQ-2A): R_t = 4.15 min.

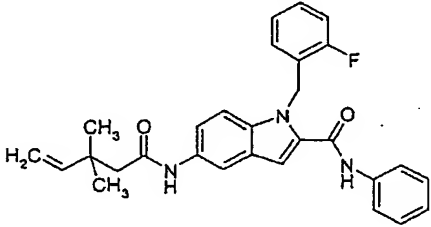
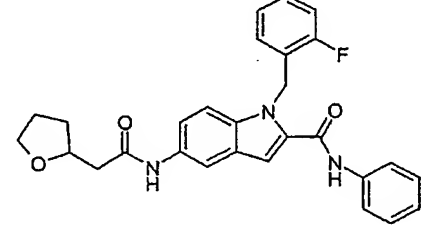
MS (ESIpos): m/z = 484.1 (M+H)⁺

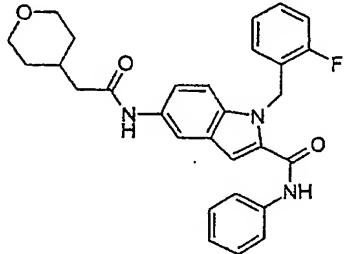
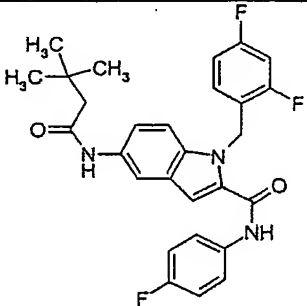
¹H-NMR (200 MHz, DMSO-d₆): δ = 1.05 (s, 3H), 1.63 (s, 8H), 2.29 (s, 2H), 5.90 (s, 2H), 6.60 (t, 1H), 6.91-7.39 (m, 9H), 7.44 (d, 1H), 7.72 (d, 2H), 8.10 (s, 1H), 9.79 (s, 1H), 10.37 (s, 1H).

20

The following compounds are prepared analogously to the procedure described in Example 26 using the appropriate starting materials:

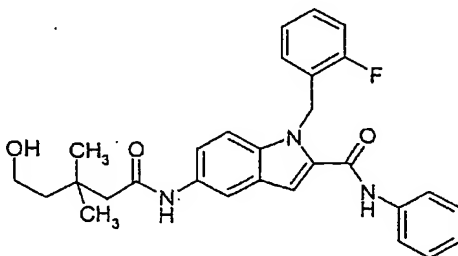
Example	Structure	Analytical data
27		<p>LC/MS (method 2): R_t = 3.90 min.</p> <p>MS (ESIpos): m/z = 470 ($M+H$)⁺.</p> <p>¹H-NMR (400 MHz, DMSO-d_6): δ = 1.20 (m, 2H), 1.52 (m, 2H), 1.59 (m, 2H), 1.77 (m, 2H), 2.20 - 2.37 (m, 3H), 5.90 (s, 2H), 6.59 (t, 1H), 7.00 (t, 1H), 7.09 (t, 1H), 7.19 (t, 1H), 7.25 (q, 1H), 7.29-7.39 (m, 4H), 7.45 (d, 1H), 7.72 (d, 2H), 8.10 (s, 1H), 9.80 (s, 1H), 10.34 (s, 1H).</p>
28		<p>LC/MS (method 2): R_t = 4.07 min.</p> <p>MS (ESIpos): m/z = 484 ($M+H$)⁺.</p> <p>¹H-NMR (400 MHz, DMSO-d_6): δ = 0.98 (q, 2H), 1.11-1.31 (m, 3H), 1.69 (m, 6H), 2.18 (d, 2H), 5.90 (s, 2H), 6.59 (t, 1H), 7.00 (t, 1H), 7.09 (t, 1H), 7.19 (t, 1H), 7.25 (q, 1H), 7.29-7.39 (m, 4H), 7.45 (d, 1H), 7.72 (d, 2H), 8.10 (s, 1H), 9.80 (s, 1H), 10.34 (s, 1H).</p>

Example	Structure	Analytical data
29		<p>LC/MS (SMKL-ZQ-2A): R_t = 3.95 min.</p> <p>MS (ESIpos): m/z = 470.2 ($M+H$)⁺.</p> <p>¹H-NMR (400 MHz, DMSO-d_6): δ = 1.14 (s, 6H), 2.29 (s, 2H), 4.94 (dd, 2H), 5.90 (s, 2H), 5.99 (dd, 1H), 6.60 (t, 1H), 7.00 (t, 1H), 7.09 (t, 1H), 7.21 (dt, 2H), 7.33 (t, 3H), 7.37 (s, 1H), 7.45 (d, 1H), 7.72 (d, 2H), 8.07 (s, 1H), 9.74 (s, 1H), 10.35 (s, 1H).</p>
30		<p>LC/MS (SMKL-ZQ-2A): R_t = 3.48 min.</p> <p>MS (ESIpos): m/z = 472.1 ($M+H$)⁺.</p> <p>¹H-NMR (200 MHz, DMSO-d_6): δ = 1.49-1.65 (m, 1H), 1.88 (t, 2H), 1.92-2.10 (m, 1H), 3.60 (q, 1H), 3.78 (q, 1H), 4.19 (quintet, 1H), 5.90 (s, 2H), 6.59 (t, 1H), 7.02 (dt, 2H), 7.22-7.53 (m, 9H), 7.73 (d, 2H), 8.11 (d, 1H), 9.88 (s, 1H), 10.37 (s, 1H).</p>

Example	Structure	Analytical data
31		<p>LC/MS (SMKL-ZQ-2A): R_t = 3.42 min.</p> <p>MS (ESIpos): m/z = 486.1 ($M+H$)⁺.</p> <p>¹H-NMR (200 MHz, DMSO-d_6): δ = 1.19-1.28 (dd, 2H), 1.61 (d, 2H), 1.99 (s, 1H), 2.25 (d, 2H), 3.25 (s, 2H), 3.83 (d, 2H), 5.90 (s, 2H), 6.59 (t, 1H), 6.97 (dt, 3H), 7.12-7.53 (m, 9H), 7.72 (d, 2H), 8.10 (d, 1H), 9.87 (s, 1H), 10.36 (s, 1H).</p>
32		<p>¹H-NMR (200 MHz, DMSO-d_6): δ = 1.04 (s, 9H), 2.19 (s, 2H), 5.85 (s, 2H), 6.70 (q, 12H), 6.94 (dt, 1H), 7.10-7.28 (m, 3H), 7.28-7.42 (m, 2H), 7.48 (d, 1H), 7.75 (dd, 2H), 8.09 (s, 1H), 9.76 (s, 1H), 10.43 (s, 1H).</p>

Example 33

1-(2-Fluorobenzyl)-5-[(5-hydroxy-3,3-dimethylpentyl)amino]-N-phenyl-1H-indole-2-carboxamide



5

60 mg (0.13 mmol) of the compound from Example 29 are dissolved in 2 ml of THF and cooled to 0°C. Over a period of 3.5 hours, a total of 0.93 ml (0.46 mmol) of a 0.5-molar 9-borabicyclo[3.3.1]nonane solution in THF is added a little at a time to this solution, and during the addition, the temperature is allowed to warm to RT. The reaction mixture is stirred at RT for a further hour and then, at 0°C, 0.5 ml each of sodium carbonate solution and hydrogen peroxide solution are added slowly. After the exothermic reaction has ended, the mixture is stirred at RT for another 30 min. The reaction mixture is then diluted with ethyl acetate and extracted with dist. water and saturated sodium chloride solution. The organic phase is dried over sodium sulphate and filtered and the solvent is removed under reduced pressure. The residue is purified chromatographically on silica gel (mobile phase: cyclohexane / ethyl acetate 5:1 to 1:1). This gives 53 mg (85% of theory) of the product.

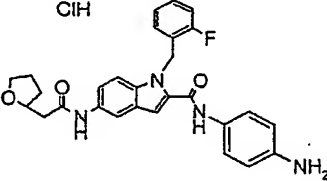
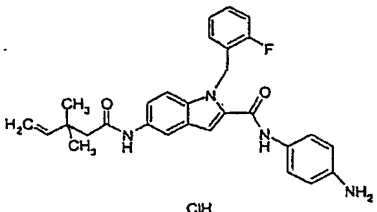
15

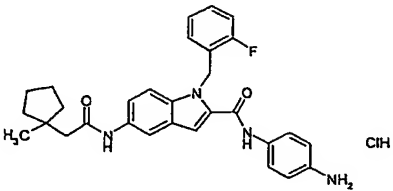
LC/MS (MHZ2P01): $R_t = 4.63$ min.

20

MS (ESIpos): $m/z = 488.2$ ($M+H$)⁺.

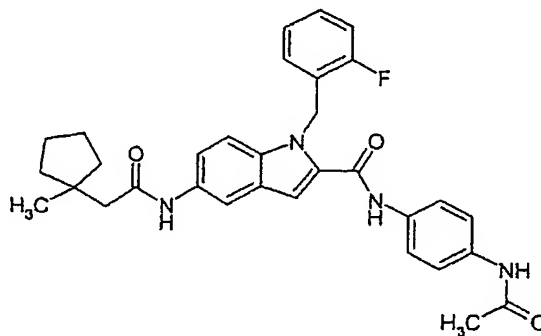
The preparation of the following compounds is carried out analogously to the procedure described in Example XXXV:

Example	Structure	Analytical data
34	<p>ClH</p> 	<p>LC/MS (method 2): $R_t = 2.25$ min</p> <p>MS (ED): $m/z = 487$ ($M+H-HCl$)⁺</p>
35	 <p>ClH</p>	<p>LC/MS (SMKL-ZQ-2A-CC): $R_t = 2.84$ min.</p> <p>MS (ESIpos): $m/z = 485.4$ ($M+H$)⁺.</p> <p>¹H-NMR (400 MHz, DMSO-d₆): $\delta = 1.14$ (s, 6H), 2.30 (s, 2H), 4.87-5.02 (m, 3H), 5.89 (s, 2H), 5.95 (s, 2H), 6.60 (dt, 2H), 7.01 (q, 2H), 7.13 (br s, 1H), 7.34 (t, 1H), 7.41 (s, 1H), 7.46 (d, 1H), 7.53 (s, 1H), 7.69 (d, 1H), 8.10 (s, 1H), 9.78 (s, 1H), 10.51 (s, 1H), 10.63 (s, 1H).</p>

Example	Structure	Analytical data
36		LC/MS (SMKL-ZQ-2A-CC): $R_t = 2.25$ min. MS (ESIpos): $m/z = 487.1$ $(M+H)^+$. $^1\text{H-NMR}$ (400 MHz, DMSO- d_6): $\delta = 1.55$ (quintet, 1H), 1.85 (q, 2H), 2.00 (quintet, 1H), 3.39 (s, 1H), 3.61 (q, 2H), 3.76 (q, 2H), 4.18 (q, 3H), 5.90 (s, 2H), 6.58 (t, 1H), 7.00 (t, 1H), 7.22 (dt, 2H), 7.36 (d, 3H), 7.43 (s, 1H), 7.47 (d, 1H), 7.85 (d, 2H), 8.14 (s, 1H), 9.92 (s, 1H), 10.56 (s, 1H).

Example 37

N-[4-(Acetylamino)phenyl]-1-(2-fluorobenzyl)-5-[[[(1-ethylcyclopentyl)acetyl]-amino]-1H-indole-2-carboxamide



- 111 -

79 mg (0.15 mmol) of the compound from Example 36 and 30 mg (0.29 mmol) of triethylamine are initially charged in 3 ml of dichloromethane, and the mixture is cooled to 0°C. 11.5 mg (0.15 mmol) of acetyl chloride are then added, and the mixture is stirred at RT overnight. The mixture is diluted with 10 ml of dichloromethane and washed successively with 1 N hydrochloric acid, aqueous sodium bicarbonate solution and water and dried over sodium sulphate, and the solvent is removed under reduced pressure. The residue is triturated with diisopropyl ether, isolated by filtration and dried.

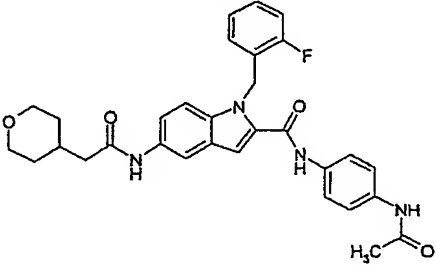
Yield: 68 mg (63% of theory)

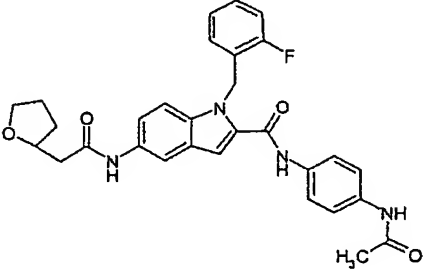
LC/MS (MHZ2P01): $R_t = 4.82$ min.

MS (ESIpos): $m/z = 541.3$ ($M+H$)⁺.

¹H-NMR (200 MHz, DMSO-d₆): $\delta = 1.07$ (s, 3H), 1.63 (s, 8H), 2.02 (s, 3H), 2.29 (s, 2H), 5.90 (s, 2H), 6.57 (t, 1H), 7.00 (t, 1H), 7.13-7.72 (m, 7H), 8.09 (s, 1H), 9.77 (s, 1H), 9.91 (s, 1H), 10.31 (s, 1H)

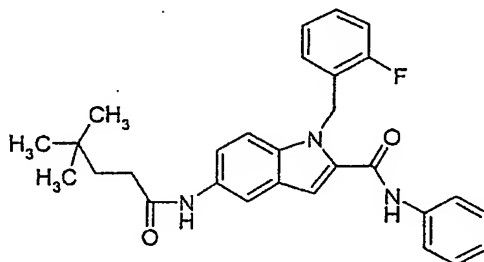
The following compounds are prepared analogously to the procedure described in Example 37:

Example	Structure	Analytical data
38		LC/MS (MHZ2P01): $R_t = 3.95$ min. MS (ESIpos): $m/z = 543.3$ (M+H) ⁺ . ¹ H-NMR (200 MHz, DMSO-d ₆): $\delta = 1.15$ (s, 1H), 2.03 (d, 8H), 2.16 (t, 1H), 2.43 (s, 3H), 2.84 (t, 2H), 5.89 (s, 2H), 6.59 (t, 1H), 7.01 (t, 1H), 7.17-7.67 (m, 9H), 8.07 (s, 1H), 9.90 (d, 2H), 10.30 (s, 1H).

Example	Structure	Analytical data
39		LC/MS (MHZ2P01): $R_t = 3.97$ min. MS (ESIpos): $m/z = 529.1$ (M+H) ⁺ .

Example 40

5-[(4,4-Dimethylpentanoyl)amino]-1-(2-fluorobenzyl)-N-phenyl-1H-indole-2-carboxamide



5

A solution of 300 mg (0.83 mmol) of the compound from Example XVI, 51 mg (0.42 mmol) of 4-dimethylaminopyridine and 240 mg (1.25 mmol) of N'-(3-dimethylaminopropyl)-N-ethylcarbodiimide \times HCl in 10 ml of DMF is initially charged. 126 mg (1.0 mmol) of 4,4-dimethyl-2-pentynoic acid (prepared according to *J. Chem. Soc. Perkin II* 1990, 1997ff.) is added, and the mixture is stirred at RT overnight. For work-up, the mixture is diluted and extracted with dichloromethane and aqueous hydrochloric acid. The organic phase is washed with sat. sodium bicarbonate solution, dried with sodium sulphate, filtered and concentrated under reduced pressure, using a rotary evaporator. The residue is purified by preparative HPLC. 258 mg of a white solid (53% of theory) are obtained, 100 mg (0.21 mmol) of which are dissolved in 5 ml of ethanol and hydrogenated at atmospheric pressure in the presence of 50 mg of Pd/activated carbon (10%) for 3 h. The solution is then filtered through Celite, and the filter cake is washed thoroughly with ethyl acetate/ethanol. The solvent is removed under reduced pressure.

15

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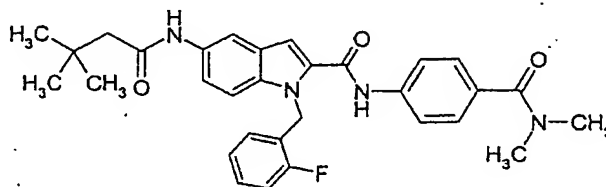
Yield: 101 mg (99% of theory)

$^1\text{H-NMR}$ (200 MHz, DMSO- d_6): δ = 0.91 (s, 9H), 1.53 (m, 2H), 2.29 (m, 2H), 5.90 (s, 2H), 6.59 (t, 1H), 7.06 (dt, 2H), 7.13-7.40 (m, 6H), 7.46 (d, 1H), 7.73 (d, 2H), 8.10 (s, 1H), 9.86 (s, 1H), 10.35 (s, 1H).

25

Example 41

N-{4-[(Dimethylamino)carbonyl]phenyl}-5-[(3,3-dimethylbutanoyl)amino]-1-(2-fluorobenzyl)-1H-indole-2-carboxamide



5

Under argon, 200 mg (0.43 mmol) of 5-[(3,3-dimethylbutanoyl)amino]-1-(2-fluorobenzyl)-1H-indole-2-carboxylic acid (Example XXXIX) are dissolved in 2 ml of DMF, and 4 ml of pyridine are added. 489.2 mg (1.29 mmol) of HATU are added to this solution, 140.8 mg (0.86 mmol) of 4-amino-N,N-dimethylbenzamide are then slowly added dropwise and the reaction mixture is stirred at RT overnight. For work-up, water is added and the mixture is extracted repeatedly with ethyl acetate. The combined organic phases are dried over sodium sulphate and filtered, and the solvent is removed under reduced pressure. The residue is purified by preparative HPLC.

15 This gives 47.4 mg (15% of theory) of product.

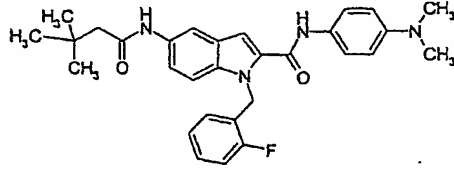
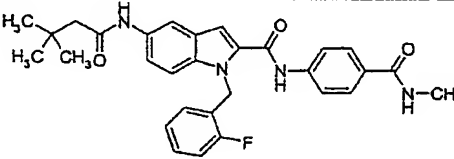
HPLC (SYA-HPPSK2): $R_t = 4.69$ min.

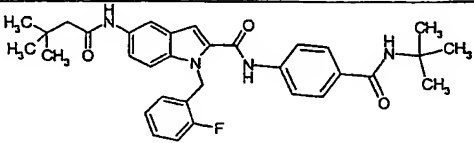
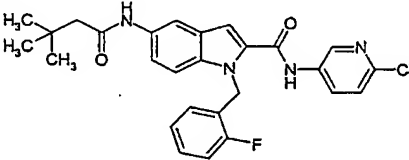
MS (ESIpos): $m/z = 529$ ($M+H$)⁺.

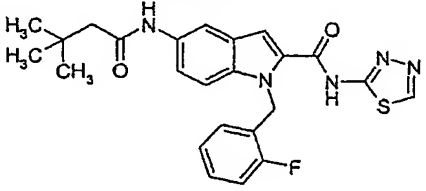
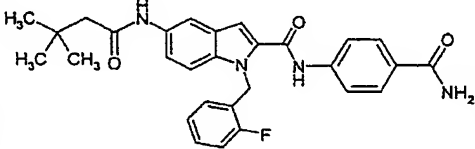
¹H-NMR (400 MHz, DMSO-d₆): $\delta = 1.04$ (s, 9H), 2.19 (s, 2H), 2.96 (s, 6H), 5.90 (s, 2H), 6.60 (t, 1H), 7.19 (t, 1H), 7.25 (q, 1H), 7.27-7.50 (m, 3H), 7.79 (d, 2H), 7.81 (s, 1H), 8.10 (s, 1H), 9.75 (s, 1H), 10.51 (d, 1H).

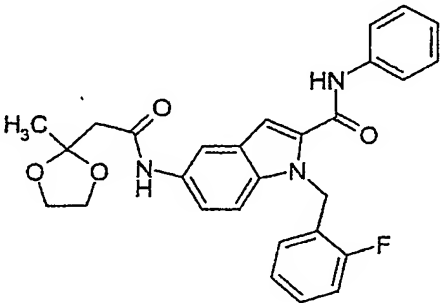
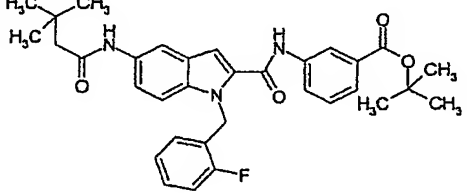
20

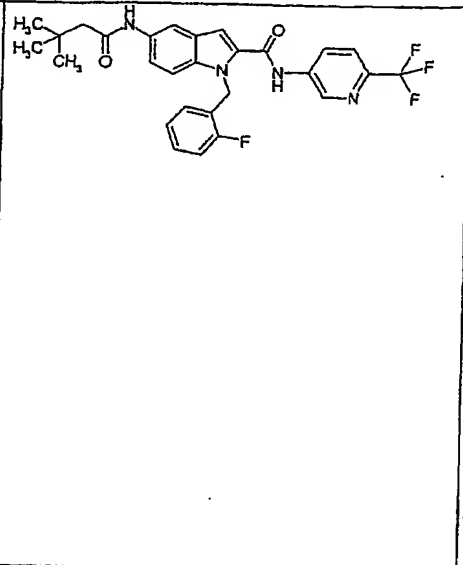
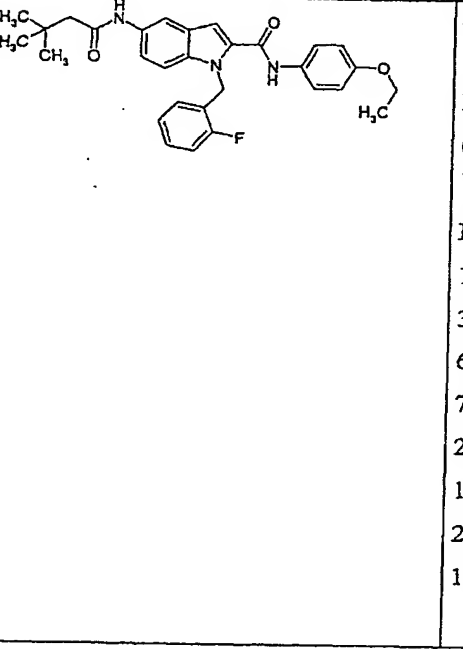
The following compounds are prepared analogously to the procedure described in Examples 26 and 41 using the appropriate starting materials:

Example	Structure	Analytical data
42		LC/MS (MHZ2P01): $R_t = 4.68$ min. MS (ESIpos): $m/z = 501.4$ ($M+H$) ⁺ . ¹ H-NMR (300 MHz, DMSO- d_6): $\delta = 1.04$ (s, 9H), 2.19 (s, 2H), 2.86 (s, 6H), 5.90 (s, 2H), 6.70 (d, 2H), 7.00 (t, 1H), 7.20 (dt, 2H), 7.30 (s, 1H), 7.33 (d, 1H), 7.41 (d, 1H), 7.51 (d, 2H), 8.05 (d, 1H), 9.69 (s, 1H), 10.06 (s, 1H).
43		LC/MS (SMKL-ZQ-2A-CC): $R_t = 3.22$ min. MS (ESIpos): $m/z = 515.2$ ($M+H$) ⁺ .

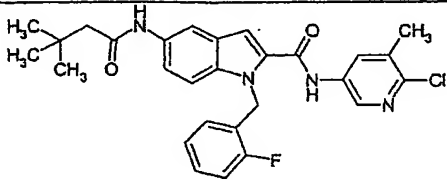
Example	Structure	Analytical Data
44		<p>HPLC (SYA-HPPSK2): $R_t = 5.09$ min.</p> <p>$^1\text{H-NMR}$ (300 MHz, CDCl_3): $\delta = 1.04$ (s, 9H), 1.38 (s, 9H), 2.19 (s, 2H), 5.90 (s, 2H), 6.61 (t, 1H), 7.00 (t, 1H), 7.22 (dt, 2H), 7.35 (d, 1H), 7.42 (d, 2H), 7.60 (s, 1H), 7.79 (s, 4H), 8.09 (d, 1H), 9.72 (s, 1H), 10.47 (s, 1H).</p>
45		<p>HPLC (SYA-HPPSK2): $R_t = 5.07$ min.</p> <p>MS (ESIpos): $m/z = 493.2$ ($\text{M}+\text{H}$)$^+$.</p> <p>$^1\text{H-NMR}$ (300 MHz, DMSO-d_6): $\delta = 10.67$ (s, 1H), 9.76 (s, 1H), 8.74 (d, 1H), 8.20 (dd, 1H), 8.12 (d, 1H), 7.5-7.45 (m, 2H), 7.43 (s, 1H), 7.38 (d, 1H), 7.33-7.14 (m, 3H), 7.0 (dt, 1H), 5.89 (s, 2H), 2.19 (s, 2H), 1.04 (s, 9H).</p>

Example	Structure	Analytical data
46		HPLC (SYA-HPPSK2): R_t = 4.67 min. MS (ESIpos): m/z = 466.1 (M+H) ⁺ . ¹ H-NMR (300 MHz, DMSO-d ₆): δ = 1.04 (s, 9H), 2.20 (s, 2H), 5.93 (s, 2H), 6.55 (t, 1H), 7.00 (t, 1H), 7.23 (dt, 2H), 7.35 (dd, 1H), 7.49 (d, 1H), 7.77 (s, 1H), 8.16 (d, 1H), 9.19 (s, 1H), 9.75 (s, 1H), 13.07 (s, 1H).
47		HPLC (SYA-HPPSK2): R_t = 4.56 min. MS (ESIpos): m/z = 501.0 (M+H) ⁺ . ¹ H-NMR (300 MHz, DMSO-d ₆): δ = 1.04 (s, 9H), 2.20 (s, 2H), 5.90 (s, 2H), 6.62 (t, 1H), 7.01 (t, 1H), 7.22 (dt, 3H), 7.36 (dd, 1H), 7.43 (d, 2H), 7.83 (q, 5H), 8.09 (d, 1H), 9.73 (s, 1H), 10.52 (s, 1H).

Example	Structure	Analytical data
50		<p>LC/MS (SMKL-ZQ-2A): R_t = 3.43 min.</p> <p>MS (ESIpos): m/z = 488.3 ($M+H$)⁺.</p> <p>¹H-NMR (200 MHz, DMSO-d_6): δ = 1.45 (s, 3H), 2.62 (s, 2H), 3.92 (d, 4H), 5.90 (s, 2H), 6.60 (t, 1H), 6.96-7.41 (m, 8H), 7.46 (d, 1H), 7.73 (d, 2H), 8.10 (d, 1H), 9.77 (s, 1H), 10.37 (s, 1H).</p>
51		<p>LC/MS (method 2): R_t = 4.82 min.</p> <p>MS (ESIpos): m/z = 558 ($M+H$)⁺.</p> <p>¹H-NMR (400 MHz, DMSO-d_6): δ = 1.05 (s, 9H), 1.56 (s, 9H), 2.19 (s, 2H), 5.90 (s, 2H), 6.60 (t, 1H), 7.02 (t, 1H), 7.22 (m, 2H), 7.36 (d, 1H), 7.44 (m, 3H), 7.63 (d, 1H), 8.00 (d, 1H), 8.10 (s, 1H), 8.28 (s, 1H), 9.77 (s, 1H), 10.54 (s, 1H).</p>

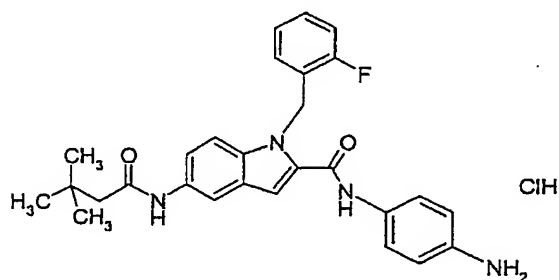
Example	Structure	Analytical data
52		<p>HPLC (SYA-HPPSK2): R_t = 5.01 min.</p> <p>MS (ESIpos): m/z = 526.9 ($M+H$)⁺.</p> <p>¹H-NMR (300 MHz, DMSO-d_6): δ = 1.04 (s, 9H), 2.20 (s, 2H), 5.90 (s, 2H), 6.62 (t, 1H), 7.01 (t, 1H), 7.16-7.29 (m, 2H), 7.38 (dd, 1H), 7.48 (t, 2H), 7.88 (d, 1H), 8.12 (d, 1H), 8.44 (dd, 1H), 9.04 (d, 1H), 9.74 (s, 1H), 10.87 (s, 1H).</p>
53		<p>HPLC (SYA-HPPSK2): R_t = 5.06 min.</p> <p>MS (ESIpos): m/z = 502 ($M+H$)⁺.</p> <p>¹H-NMR (300 MHz, DMSO-d_6): δ = 1.04 (s, 9H), 1.31 (t, 3H), 2.19 (s, 2H), 3.99 (q, 2H), 5.89 (s, 2H), 6.60 (t, 1H), 6.88 (d, 2H), 7.0 (t, 1H), 7.14-7.28 (m, 2H), 7.32 (s, 1H), 7.34 (d, 1H), 7.43 (d, 1H), 7.60 (d, 2H), 8.06 (d, 1H), 9.70 (s, 1H), 10.20 (s, 1H).</p>

Example	Structure	Analytical data
54		<p>HPLC (method 1): R_t = 5.376 min.</p> <p>MS (ESIpos): m/z = 530 ($M+H$)⁺.</p> <p>¹H-NMR (200 MHz, DMSO-d_6): δ = 1.04 (s, 9H), 1.33 (t, 3H), 2.19 (s, 2H), 4.33 (q, 2H), 5.92 (s, 2H), 6.61 (t, 1H), 7.0 (t, 1H), 7.15-7.40 (m, 3H), 7.49 (m, 3H), 7.68 (d, 1H), 8.04 (d, 1H), 8.12 (d, 1H), 9.70 (s, 1H), 10.58 (s, 1H).</p>
55		<p>HPLC (SYA-HPPSK2): R_t = 4.71 min.</p> <p>MS (ESIpos): m/z = 488.9 ($M+H$)⁺.</p> <p>¹H-NMR (300 MHz, DMSO-d_6): δ = 1.04 (s, 9H), 2.19 (s, 2H), 3.83 (s, 3H), 5.89 (s, 2H), 6.61 (t, 1H), 6.82 (s, 1H), 7.0 (t, 1H), 7.15-7.32 (m, 3H), 7.36 (s, 1H), 7.44 (d, 1H), 7.99 (dd, 1H), 8.09 (s, 1H), 8.45 (d, 1H), 9.71 (s, 1H), 10.37 (s, 1H).</p>

Example	Structure	- Analytical data
56		<p>HPLC (SYA-HPPSK2): R_t = 5.14 min.</p> <p>MS (ESIpos): m/z = 507 ($M+H$)⁺.</p> <p>¹H-NMR (300 MHz, DMSO-d_6): δ = 1.04 (s, 9H), 2.14 (s, 2H), 2.34 (s, 3H), 5.89 (s, 2H), 6.59 (t, 1H), 7.0 (t, 1H), 7.13-7.29 (m, 2H), 7.35 (dd, 1H), 7.42 (s, 1H), 7.45 (d, 1H), 8.10 (d, 1H), 8.18 (d, 1H), 8.56 (d, 1H), 9.72 (s, 1H), 10.59 (s, 1H).</p>

Example 57

- 5 N-(4-Aminophenyl)-5-[(3,3-dimethylbutanoyl)amino]-1-(2-fluorobenzyl)-1H-indole-2-carboxamide hydrochloride



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104 mg (0.18 mmol) of tert-butyl 4-({[5-[3,3-dimethylbutanoyl]amino]-1-(2-fluorobenzyl)-1H-indol-2-yl]carbonyl}amino)phenylcarbamate (Example XLV) are taken up in 1 ml of dioxane and 1 ml of concentrated hydrochloric acid, and the mixture is stirred at RT for 1 h. The solvent is removed under reduced pressure and the crystals that remain are filtered off and dried. This gives 92.5 mg (75%) of the product.

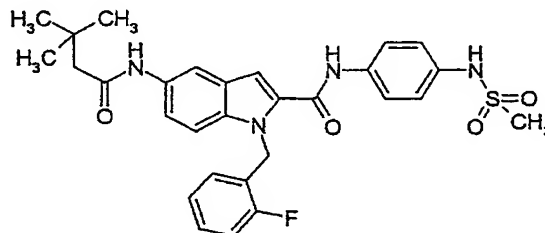
LC/MS (SMKL-ZQ-2): $R_t = 3.09$ min.

MS (ESIpos): $m/z = 473$ ($M+H$)⁺

¹H-NMR (200 MHz, DMSO-d₆): $\delta = 1.04$ (s, 9H), 1.47 (s, 9H), 2.19 (s, 2H), 5.90 (s, 2H), 6.56 (t, 1H), 7.00 (dt, 1H), 7.16-7.49 (m, 7H), 7.59 (d, 2H), 8.08 (s, 1H), 9.31 (s, 1H), 9.75 (s, 1H), 10.26 (s, 1H).

Example 58

5-[(3,3-Dimethylbutyl)amino]-1-(2-fluorobenzyl)-N-{4-[(methanesulphonyl)amino]-phenyl}-1H-indole-2-carboxamide



22.5 mg (0.20 mmol) of methanesulphonyl chloride are dissolved in 1 ml of dichloromethane, and 38.9 mg (0.49 mmol) of pyridine are added. A solution of 100 mg (0.20 mmol) of N-(4-aminophenyl)-5-[(3,3-dimethylbutyl)amino]-1-(2-fluorobenzyl)-1H-indole-2-carboxamide hydrochloride (Example 57) in 1 ml of dichloromethane is added dropwise to this mixture, and the reaction mixture is stirred at RT overnight. For work-up, 22 ml of 1-molar hydrochloric acid are added, and the mixture is extracted repeatedly with dichloromethane. The combined organic phases are washed in each case once with saturated copper sulphate solution, saturated sodium bicarbonate solution and water. They are then dried over sodium sulphate and

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filtered, and the solvent is removed under reduced pressure. This gives 96.2 mg (73%) of the product.

LC/MS (MHZ2P01): $R_t = 4.81$ min.

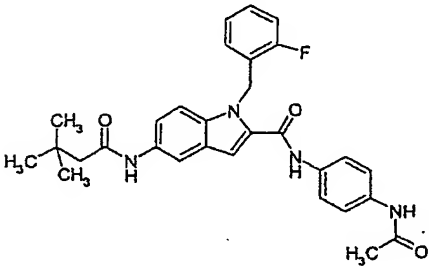
MS (ESIpos): $m/z = 551$ ($M+H$)⁺.

- 5 ¹H-NMR (400 MHz, DMSO-d₆): $\delta = 1.04$ (s, 9H), 2.19 (s, 2H), 2.94 (s, 3H), 5.89 (s, 2H), 6.58 (t, 1H), 7.00 (t, 1H), 7.14-7.29 (m, 4H), 7.34 (d, 2H), 7.45 (d, 1H), 7.68 (d, 2H), 8.09 (s, 1H), 9.58 (s, 1H), 9.73 (s, 1H), 10.35 (s, 1H).

- 10 The following compound is prepared analogously to the procedure described in Example 58:

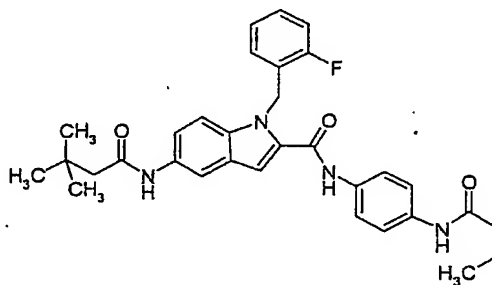
Example	Structure	Analytical data
59		<p>LC/MS (MHZ2Q01): $R_t = 4.91$ min.</p> <p>MS (ESIpos): $m/z = 593$ ($M+H$)⁺.</p> <p>¹H-NMR (400 MHz, DMSO-d₆): $\delta = 0.83$ (t, 3H), 1.04 (s, 9H), 1.33 (m, 2H), 1.62 (m, 2H), 2.19 (s, 2H), 2.95 (m, 2H), 5.89 (s, 2H), 6.58 (t, 1H), 7.00 (t, 1H), 7.03-7.37 (m, 5H), 7.43 (d, 2H), 7.59 (m, 2H), 8.08 (s, 1H), 9.72 (s, 1H), 10.26 (s, 1H).</p>

- 15 The following compound is prepared analogously to the procedure described in Example 37 using Example 57 as starting material:

Example	Structure	Analytical data
60		LC/MS (MHZ2Q01): $R_t = 4.45$ min. MS (ESIpos): $m/z = 515$ ($M+H$) ⁺ . ¹ H-NMR (200 MHz, DMSO- d_6): $\delta = 1.04$ (s, 9H), 2.02 (s, 3H), 2.19 (s, 2H), 6.00 (s, 2H), 6.58 (dt, 1H), 7.00 (dt, 1H), 7.11-7.48 (m, 5H), 7.52 (d, 2H), 7.64 (d, 2H), 8.09 (s, 1H), 9.75 (s, 1H), 9.91 (s, 1H), 10.31 (s, 1H).

Example 61

N-[4-(Butyrylamino)phenyl]-5-[(3,3-dimethylbutyl)amino]-1-(2-fluorobenzyl)-1H-indole-2-carboxamide



84 mg (0.14 mmol) of ethyl-2-({[4-({[5-(3,3-dimethylbutanoyl)amino]-1-(2-fluorobenzyl)-1H-indol-2-yl]carbonyl}amino)phenyl]amino}carbonyl)butanoate (Example XLVI) and 6.5 mg (0.27 mmol) of lithium hydroxide are taken up in 0.5 ml of methanol and 0.5 ml of THF, and the mixture is heated at 90°C for 30 min. For

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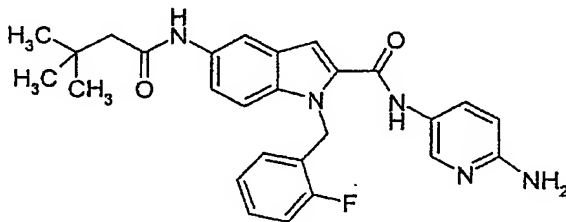
work-up, the cold reaction mixture is diluted with ethyl acetate and extracted in each case once with 1-molar hydrochloric acid and saturated sodium chloride solution. The organic phase is dried over sodium sulphate and filtered, and the solvent is removed under reduced pressure. The residue is triturated with diethyl ether/
5 dichloromethane and the resulting solid is filtered off. The crude product is purified by preparative HPLC. This gives 4.9 mg (7% of theory) of the product.

LC/MS (SMKL-ZQ-2A-CC): $R_t = 3.54$ min.

MS (ESIpos): $m/z = 543.2$ ($M+H$)⁺.

10 **Example 62**

N-(6-Amino-3-pyridinyl)-5-[(3,3-dimethylbutanoyl)amino]-1-(2-fluorobenzyl)-1H-indole-2-carboxamide



15 107 mg (0.12 mmol) of di-(tert-butyl) 5-([5-[(3,3-dimethylbutanoyl)amino]-1-(2-fluorobenzyl)-1H-indol-2-yl]carbonyl)amino)-2-pyridinylimidedicarbonate (Example XLII) are suspended in 2 ml of dichloromethane/trifluoroacetic acid (1:1), and the mixture is stirred at RT overnight. The solvent is removed under reduced pressure, the residue is taken up in water and the pH is adjusted to 7-8 using 1-molar
20 sodium hydroxide solution. The mixture is extracted repeatedly with ethyl acetate, the combined organic phases are dried over sodium sulphate and filtered and the solvent is removed under reduced pressure. The crude product is purified by preparative HPLC. This gives 48 mg (83%) of the product.

HPLC (SYA-HPPSK2): $R_t = 4.47$ min.

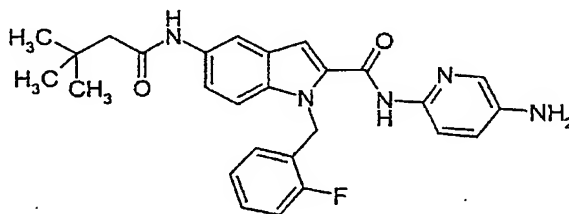
25 MS (ESIpos): $m/z = 474.0$ ($M+H$)⁺.

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$^1\text{H-NMR}$ (200 MHz, DMSO-d_6): δ = 1.04 (s, 9H), 2.19 (s, 2H), 5.81 (s, 2H), 5.89 (s, 2H), 6.43 (d, 1H), 6.56 (t, 1H), 7.00 (t, 1H), 7.12-7.48 (m, 5H), 7.65 (d, 1H), 8.12 (d, 2H), 9.74 (s, 1H), 10.10 (s, 1H).

5 **Example 63**

N-(5-Amino-2-pyridinyl)-5-[(3,3-dimethylbutanoyl)amino]-1-(2-fluorobenzyl)-1H-indole-2-carboxamide



10

46.8 mg (0.19 mmol) of hydrogen bromide (33% strength solution in acetic acid) are added to 29 mg (0.05 mmol) of benzyl 6-({[5-[(3,3-dimethylbutanoyl)amino]-1-(2-fluorobenzyl)-1H-indol-2-yl]carbonyl}amino)-3-pyridinylcarbamate (Example XLIII), and the mixture is stirred at RT overnight. The solvent is removed under reduced pressure and the residue is purified by preparative HPLC. This gives 6 mg (27%) of the product.

15

LC/MS (MHZ2P01): R_t = 3.98 min.

MS (ESIpos): m/z = 474.3 ($\text{M}+\text{H}$) $^+$.

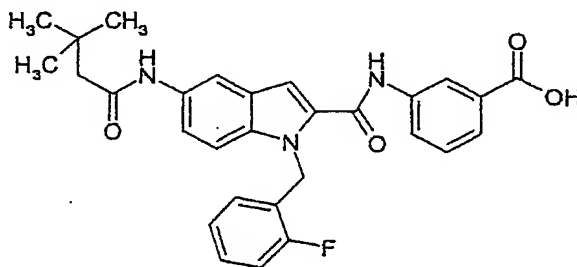
$^1\text{H-NMR}$ (300 MHz, DMSO-d_6): δ = 1.04 (s, 9H), 2.19 (s, 2H), 5.14 (s, 2H), 5.91 (s, 2H), 6.52 (t, 1H), 6.99 (t, 1H), 7.14-7.29 (m, 3H), 7.30 (d, 1H), 7.49 (s, 1H), 7.69 (d, 1H), 7.73 (d, 1H), 8.08 (d, 1H), 9.69 (s, 1H), 10.32 (s, 1H).

20

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Example 64

3-({[5-[(3,3-dimethylbutanoyl)amino]-1-(2-fluorobenzyl)-1H-indol-2-yl]carbonyl}-amino)benzoic acid



5

0.3 ml of trifluoroacetic acid is added to a solution of 182 mg (0.32 mmol) of the compound from Example 51 in 1 ml of dichloromethane. The mixture is stirred at RT for 1 h and concentrated under reduced pressure.

10 Yield: 163 mg (100% of theory).

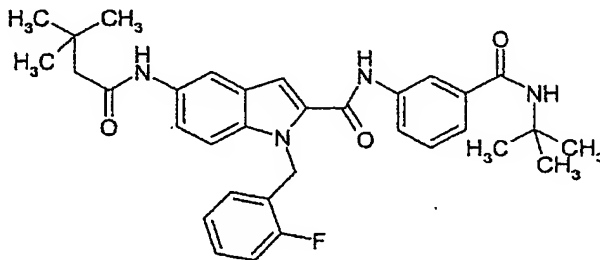
LC/MS (MHZ2P01): $R_t = 4.60$ min.

MS (ESIpos): $m/z = 502$ ($M+H$)⁺.

¹H-NMR (300 MHz, DMSO-d₆): $\delta = 1.04$ (s, 9H), 2.19 (s, 2H), 5.90 (s, 2H), 6.62 (t, 1H), 6.99 (t, 1H), 7.14-7.30 (m, 2H), 7.34 (dd, 1H), 7.44 (m, 3H), 7.65 (d, 1H), 7.97
15 (d, 1H), 8.09 (d, 1H), 8.38 (s, 1H), 9.71 (s, 1H), 10.48 (s, 1H).

Example 65

N-{3-[(tert-Butylamino)carbonyl]phenyl}-5-[(3,3-dimethylbutanoyl)amino]-1-(2-fluorobenzyl)-1H-indole-2-carboxamide



5

20 mg (0.04 mmol) of the compound from Example 64, 11.5 mg (0.06 mmol) of N'-(3-dimethylaminopropyl)-N-ethylcarbodiimide \times HCl and 2.5 mg (0.02 mmol) of 4-dimethylaminopyridine are initially charged in 1 ml of dichloromethane. 3.5 mg (0.05 mmol) of tert-butylamine are added, and the mixture is stirred at RT overnight. For work-up, the mixture is diluted and extracted with aqueous hydrochloric acid and dichloromethane. The organic phase is washed with sat. sodium chloride solution, dried with sodium sulphate, filtered and dried under reduced pressure. Purification is carried out by chromatography on silica gel.

15 Yield: 10 mg (45% of theory)

LC/MS (method 2): $R_t = 3.82$ min.

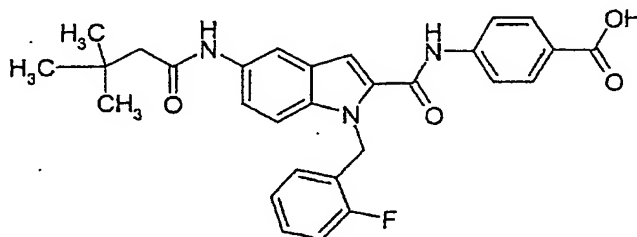
MS (ESIpos): $m/z = 557$ ($M+H$) $^+$.

1H -NMR (300 MHz, DMSO- d_6): $\delta = 1.04$ (s, 9H), 1.41 (s, 9H), 2.20 (s, 2H), 5.91 (s, 2H), 6.60 (t, 1H), 6.99 (t, 1H), 7.25 (m, 2H), 7.40 (m, 4H), 7.62 (s, 1H), 7.86 (d, 1H), 8.09 (d, 2H), 9.71 (s, 1H), 10.41 (s, 1H).

20

Example 66

4-({[5-[(3,3-Dimethylbutanoyl)amino]-1-(2-fluorobenzyl)-1H-indol-2-yl]carbonyl}-amino)benzoic acid



5

912.6 mg (2.4 mmol) of HATU and 1.24 g (6.4 mmol) of tert-butyl 4-aminobenzoate are added to a suspension of 1.0 g (0.8 mmol) of the substance from Example XLI in 21 ml of pyridine/DMF (2:1), and the reaction mixture is shaken at RT overnight.

10 The resin is filtered off with suction and washed with DMF, ethanol (30%), water, DMF, methanol and dichloromethane. To remove the polymer, the bound product is suspended in dichloromethane/trifluoroacetic acid (1:1) and shaken at RT for 30 min.

The free polymer is filtered off with suction and washed with dichloromethane, and the filtrate is freed from the solvent under reduced pressure. The residue is purified

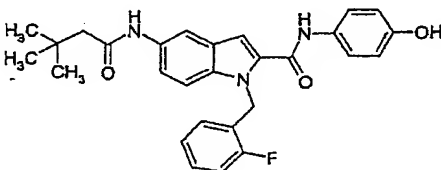
15 chromatographically on silica gel (mobile phase: dichloromethane/methanol 5:1). This gives 127 mg (32% of theory) of the product.

LC/MS (MHZ2P): $R_t = 4.39$ min.

MS (ESIpos): $m/z = 502.3$ ($M+H$)⁺.

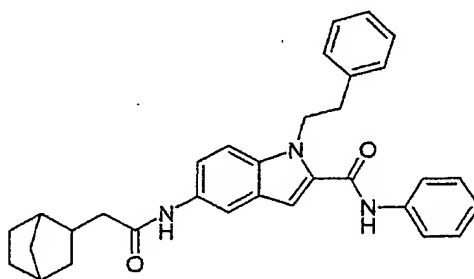
20 The following compound is prepared analogously to the procedure described in Example 66:

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Example	Structure	Analytical data
67		LC/MS (MHZ2P01): $R_t = 4.86$ min. MS (ESIpos): $m/z = 474.3$ ($M+H$) ⁺ . ¹ H-NMR (300 MHz, DMSO- <i>d</i> ₆): $\delta = 1.04$ (s, 9H), 2.19 (s, 2H), 5.89 (s, 2H), 6.59 (t, 1H), 6.71 (d, 2H), 7.00 (t, 1H), 7.18-7.38 (m, 4H), 7.40 (s, 1H), 7.47 (d, 2H), 7.95 (s, 1H), 8.07 (d, 1H), 9.22 (br s, 1H), 6.70 (s, 1H), 10.11 (s, 1H).

Example 68

5-[(Bicyclo[2.2.1]hept-2-ylacetyl)amino]-N-phenyl-1-(2-phenylethyl)-1H-indole-2-carboxamide



Under argon, 78 mg (0.22 mmol) of 5-amino-N-phenyl-1-(2-phenylethyl)-1H-indole-2-carboxamide (Example LI) are dissolved in 2 ml of THF, and 24.4 mg (0.24 mmol) of triethylamine are added. The solution is cooled to 0°C, and a solution of 37.9 mg (0.22 mmol) of bicyclo[2.2.1]hept-2-ylacetyl chloride in 0.2 ml of THF is added

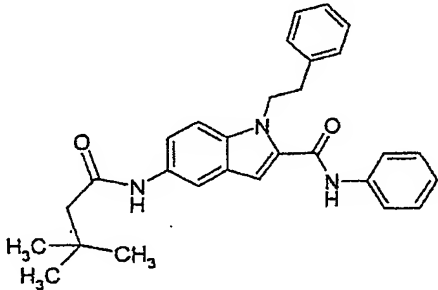
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dropwise. The reaction mixture is stirred at RT for 2 h and then diluted with 1-molar hydrochloric acid and extracted repeatedly with ethyl acetate. The combined organic phases are washed twice with saturated sodium chloride solution and once with sodium bicarbonate solution, dried over sodium sulphate and filtered. The residue obtained after removal of the solvent under reduced pressure is purified chromatographically on silica gel (mobile phase: dichloromethane/ethyl acetate). 31.5 mg (29% of theory) of the product are obtained.

LC/MS (MHZ2P): $R_t = 5.17$ min.

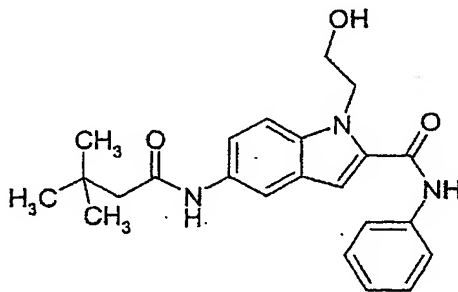
MS (ESIpos): $m/z = 492$ ($M+H$)⁺.

The following compound is prepared analogously to the procedure described in Example 68, using the starting material from Example LI:

Example	Structure	Analytical data
69		LC/MS (MHZ2P): $R_t = 4.95$ min MS (ESIpos): $m/z = 454.5$ ($M+H$) ⁺

Example 70

5-[(3,3-Dimethylbutanoyl)amino]-1-(2-hydroxyethyl)-N-phenyl-1H-indole-2-carboxamide



5

50 mg (0.12 mmol) of the compound from Example LV are dissolved in 5 ml of methanol. A total of 77.4 mg (2.05 mmol) of sodium borohydride are added a little at a time, over a period of several hours, at RT. The reaction mixture is stirred overnight at this temperature and then diluted with 1-molar hydrochloric acid and extracted repeatedly with ethyl acetate. The combined organic phases are dried over sodium sulphate and filtered and the solvent is removed under reduced pressure. This gives 38 mg (84% of theory) of the product.

10

LC/MS (MHZ2P01): $R_t = 4.14$ min.

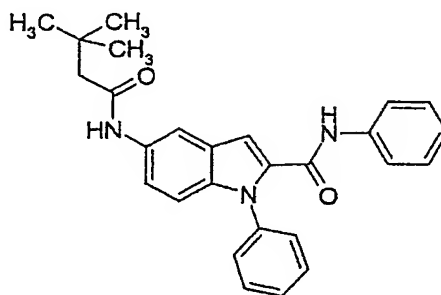
15

MS (ESIpos): $m/z = 394.3$ ($M+H$)⁺.

¹H-NMR (200 MHz, DMSO-d₆): $\delta = 1.04$ (s, 9H), 2.19 (s, 2H), 3.69 (q, 2H), 4.57 (t, 2H), 4.88 (t, 1H), 7.10 (t, 1H), 7.22 (s, 1H), 7.25-7.63 (m, 4H), 7.77 (d, 2H), 8.06 (d, 1H), 9.72 (s, 1H), 10.32 (s, 1H).

Example 71

5-[(3,3-Dimethylbutanoyl)amino]-N,1-diphenyl-1H-indole-2-carboxamide



5

7.9 mg (0.09 mmol) of aniline are added to a solution of 27 mg (0.08 mmol) of 5-[(3,3-dimethylbutanoyl)amino]-1-phenyl-1H-indole-2-carboxylic acid (Example LIX), 4.7 mg (0.09 mmol) of DMAP and 22.2 mg (0.12 mmol) of EDC in 2 ml of dichloromethane, and the mixture is stirred at RT for 3 h. For work-up, 1-molar hydrochloric acid is added and the mixture is extracted repeatedly with dichloromethane. The combined organic phases are washed with saturated sodium bicarbonate solution and water, dried over sodium sulphate and filtered. Removal of the solvent under reduced pressure gives 35 mg (99% of theory) of the product.

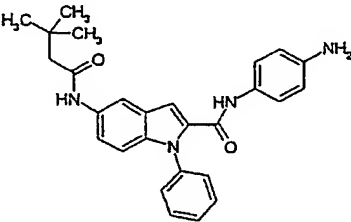
15 LC/MS (MHZ2Q01): $R_t = 4.85$ min.MS (ESIpos): $m/z = 426.4$ ($M+H$)⁺.

¹H-NMR (200 MHz, DMSO-d₆): $\delta = 1.04$ (s, 9H), 2.20 (s, 2H), 7.05-7.15 (m, 2H), 7.29-7.41 (m, 6H), 7.44-7.60 (m, 3H), 7.65 (d, 2H), 8.15 (d, 1H), 9.79 (s, 1H), 10.43 (s, 1H).

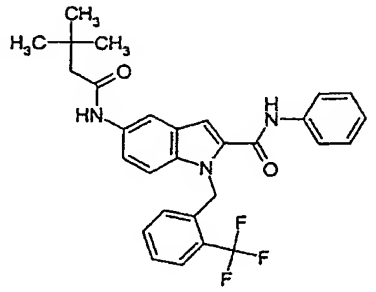
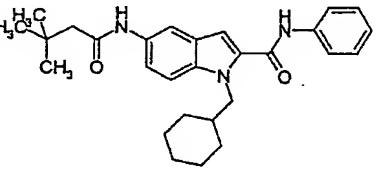
20

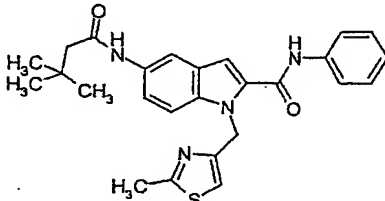
The following compound is prepared analogously to the procedure described in Preparation Example 57:

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Example	Structure	Analytical data
72		LC/MS (MHZ2Q01): $R_t = 3.78$ min. MS (ESIpos): $m/z = 441.4$ ($M+H$) ⁺ . ¹ H-NMR (200 MHz, DMSO- d_6): $\delta = 1.04$ (s, 9H), 2.20 (s, 2H), 7.09 (d, 1H), 7.22 (d, 3H), 7.29-7.56 (m, 8H), 7.73 (d, 2H), 8.17 (s, 1H), 9.81 (s, 1H), 10.57 (s, 1H).

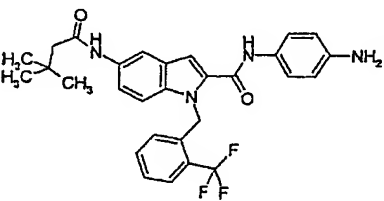
The following compounds are prepared analogously to the procedure described in Examples 26 and 41, using the appropriate starting materials:

Example	Structure	Analytical data
73		<p>LC/MS (MHZ2P01): $R_t = 5.19$ min.</p> <p>MS (ESIpos): $m/z = 508$ (M+H)⁺.</p> <p>¹H-NMR (200 MHz, DMSO-d₆): δ = 1.04 (s, 9H), 2.19 (s, 2H), 6.04 (s, 2H), 6.21 (m, 1H), 7.07 (t, 1H), 7.17-7.56 (m, 8H), 7.69 (d, 2H), 7.79 (m, 1H), 8.17 (s, 1H), 9.78 (s, 1H), 10.38 (s, 1H).</p>
74		<p>LC/MS (MHZ2P01): $R_t = 5.47$ min.</p> <p>MS (ESIpos): $m/z = 446.4$ (M+H)⁺.</p> <p>¹H-NMR (200 MHz, DMSO-d₆): δ = 0.98-1.13 (m, 13H), 1.32-1.49 (m, 2H), 1.50-1.69 (m, 3H), 2.19 (s, 2H), 4.43 (d, 2H), 7.10 (t, 1H), 7.21 (s, 1H), 7.31-7.42 (m, 3H), 7.52 (d, 1H), 7.76 (d, 2H), 8.02 (d, 1H), 9.72 (s, 1H), 10.32 (s, 1H).</p>

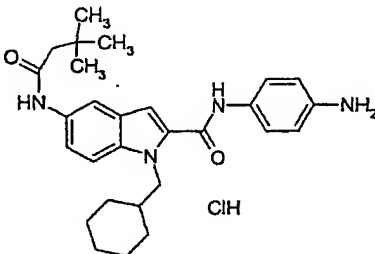
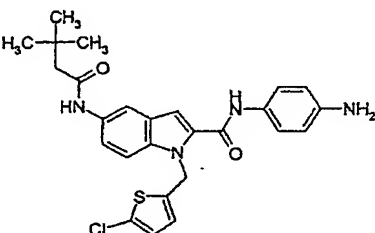
Example	Structure	Analytical data
75		LC/MS (SMKL-ZQ-2A): $R_t = 3.53$ min. MS (ESIpos): $m/z = 461.1$ ($M+H$) ⁺ . ¹ H-NMR (400 MHz, DMSO- d_6): $\delta = 1.04$ (s, 9H), 2.19 (s, 2H), 2.54 (s, 3H), 5.76 (s, 1H), 6.96 (s, 1H), 7.10 (t, 1H), 7.28 (s, 1H), 7.35 (t, 4H), 7.57 (d, 1H), 7.76 (d, 2H), 8.03 (s, 1H), 9.72 (s, 1H), 10.36 (s, 1H).

The following compounds are prepared analogously to the procedure described in Example XXXV:

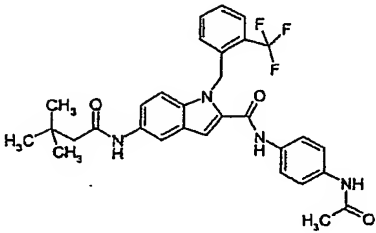
5

Example	Structure	Analytical data
76		LC/MS (MHZ2P01): $R_t = 5.19$ min. MS (ESIpos): $m/z = 508$ ($M+H$) ⁺ . ¹ H-NMR (200 MHz, DMSO- d_6): $\delta = 1.04$ (s, 9H), 2.20 (s, 2H), 6.03 (s, 2H), 6.13-6.28 (m, 1H), 7.11 (d, 2H), 7.19-7.47 (m, 4H), 7.50 (s, 1H), 7.69 (d, 2H), 7.75-7.85 (m, 1H), 8.18 (s, 1H), 9.79 (s, 1H), 10.43 (s, 1H).

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Example	Structure	Analytical data
77		<p>LC/MS (MHZ2P01): $R_t = 4.40$ min.</p> <p>MS (ESIpos): $m/z = 461.4$ ($M+H$)⁺.</p> <p>¹H-NMR (200 MHz, DMSO-d_6): $\delta = 1.04$ (s, 14H), 1.42 (br d, 2H), 1.51-1.73 (m, 4H), 3.88 (br s, 2H), 4.45 (d, 2H), 7.25 (s, 1H), 7.35 (d, 4H), 7.53 (d, 1H), 7.87 (d, 2H), 8.05 (s, 1H), 9.76 (s, 1H), 10.50 (s, 1H).</p>
78		<p>LC/MS (SMKL-ZQ-2A): $R_t = 3.09$ min.</p> <p>MS (ESIpos): $m/z = 495.1$ ($M+H$)⁺.</p> <p>¹H-NMR (400 MHz, DMSO-d_6): $\delta = 1.04$ (s, 9H), 2.19 (s, 2H), 4.97 (s, 2H), 5.89 (s, 2H), 6.56 (d, 2H), 6.90 (d, 1H), 7.03 (d, 1H), 7.24 (s, 1H), 7.37 (t, 3H), 7.65 (d, 1H), 8.02 (s, 1H), 9.72 (s, 1H), 10.00 (s, 1H).</p>

The following compound is prepared analogously to the procedure described in Example 37:

Example	Structure	Analytical structure
79		LC/MS (SMKL-ZQ-2A): $R_t = 3.60$ min. MS (ESIpos): $m/z = 565 (M+H)^+$. $^1\text{H-NMR}$ (200 MHz, DMSO-d_6): δ = 1.04 (s, 9H), 2.01 (s, 3H), 2.19 (s, 2H), 6.03 (s, 2H), 6.19 (d, 1H), 7.27 (q, 4H), 7.39-7.63 (m, 5H), 7.78 (t, 1H), 8.16 (s, 1H), 9.77 (s, 1H), 9.90 (s, 1H), 10.31 (s, 1H).